"DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE BILAYER TABLETS OF CARVEDILOL"

A dissertation submitted to

THE TAMILNADU Dr. M.G.R.MEDICAL UNIVERSITY, CHENNAI.

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MASTER OF PHARMACY

IN

PHARMACEUTICS

BY

REG. NO: 26091388

Under the guidance of

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This is to certify that the investigation in this thesis entitled **"Development and Evaluation of Sustained Release Bilayer Tablets of Carvedilol** submitted to the Tamil Nadu Dr. M.G.R Medical University, Chennai, for the partial fulfillment of the award of Degree of **Master of pharmacy** in **Pharmaceutics,** was carried out by **Regd. No. 26091388** in the Department of Pharmaceutics. **The Erode College of Pharmacy and Research Institute**, **Erode 638112**, under my guidance and supervision.

This work is original and has not been submitted in part or full to any other degree or diploma of this or any other university.

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ENDORSEMENT BY THE PRINCIPAL

This is to certify that the investigation in this thesis entitled **"Development and Evaluation of Sustained Release Bilayer Tablets of Carvedilol",** submitted in partial fulfillment for the award of degree of **Master of Pharmacy** in **Pharmaceutics,** were carried out in the laboratories of The Erode College of Pharmacy & Research Institute, Erode, by **Reg., No., 26091388** under the guidance of **Mrs. S. Allimalarkodi, M. Pharm., M.Sc Bioinformatics., Asst. Professor** in the Department of Pharmaceutics. The Erode College of Pharmacy and Research Institute, Erode 638112.

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DECLARATION

The research work embodied in this dissertation work entitled "**Development and Evaluation of Sustained Release Bilayer Tablets of Carvedilol"** was carried out by me in **Department of Pharmaceutics, The Erode College of Pharmacy & Research Institute, Erode**, under the direct supervision of **Mrs. S.Allimalarkodi, M. Pharm., M.Sc. Bioinformatics., Asst. Professor** Department of Pharmaceutics, The Erode College of Pharmacy & Research Institute, Erode – 638112.

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The work is original and has not been submitted in part or full for the award for any other Degree or Diploma of this or any other University.

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INDEX

LIST OF ABBREVATIONS

%CDR	:	Percentage Cumulative Drug Release
%DR	:	Percentage Drug Release
(t_p)	:	time of peak plasma concentration
(τ)	:	dosing interval
ACE	:	Angiotensin Converting Enzyme
BNP	:	B-type Natriuretic Peptide level
CHF	:	Congestive heart failure
cm	:	centimeter
C_{ss}	:	Concentration at steady-state
CVA	:	Cerebrovascular Accident
DASH	:	Dietary Approaches to Stop Hypertension
D_i	:	initial Dose
D_m	:	maintenance Dose
DMSO	:	Dimethyl Sulfoxide
ECG	:	Electrocardiogram
ED	:	Effective Dose
Fig	:	Figure
FTIR	:	Fourier Transform Infrared Radiation
GIT	:	Gastro Intestinal Tract
gm	:	gram
HCTZ	:	Hydrochlorothiazide
Hg	:	mercury
hr	:	hour
HTN	:	Hypertension
ICH	:	International Conference on Harmonization
IR	:	Infrared Spectroscopy
K_e	:	elimination rate Constant
kg	:	kilogram

Kpa	:	a kilopascal
K_s	:	desired release rate
LD	:	Lethal Dose
MDDS	:	Modified Drug Release
MEC	:	Minimum Effective Concentration
mg	:	milligram
mg/ml	:	milligram/millilitre
mins	:	minutes
ml	:	millilitre
mm	:	millimeter
mmHg	:	millimeter mercury
nm	:	nanometer
no	:	number
NSAID	:	Non Steroidal Anti Inflammatory Drug
PVP	:	Polyvinyl Pyrrolidone
R^2	:	Regression coefficient
rpm	:	rotations per minute
sec	:	second
SR	:	Sustained Release
SRDDS	:	Sustained Release Drug Delivery system
$t_{1/2}$	:	elimination Half life
TPR	:	Total Peripheral Resistance
USP	:	United States of Pharmacopoeia
UV	:	UltraViolet
W/V	:	Weight/Volume
W/W	:	Weight/Weight
λ_{max}	:	absorption maxima

LIST OF PHOTOGRAPHS AND GRAPHS

LIST OF TABLES

LIST OF SPECTRA

1. INTRODUCTION

Drug delivery is the method of process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient covinenience and compliance. Drug release is from diffusion, degradation, swelling and affinity based mechanisms. Most common routes of administration include the preffered non-invasive peroral (through the mouth), topical (skin), transmucosal (nasal, buccal/ sublingual, vaginal, ocular and rectal) and inhalation routes. Many medications such as peptides and proteins, antibodies, vaccines and gene based drugs, in general may not be delivered using these routes because they might be susceptible to enzymatic degradation or cannot be absorbed in to the systemic circulation efficiently due to molecular size and charge issues to be therapeutically effective. For this reason many protein and peptide drugs have to be delivered by injection or a nanoneedle array.

Current efforts in the area of drug delivery include the development of targeted delivery in which the drug is only active in the target area of the body and sustained release formulations in which the drug is released over a period of time in a controlled manner from a formulation.

1.1 SUSTAINED RELEASE DOSAGE FORM: [1, 2]

Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over extended period of after administration of a single dose. In case of injectable dosage forms, this period may vary from days to months. In the case of orally administrator forms, however this period is measured in hours and critically depends on residence time of the dosage formsin the gastro intestinal tract. The term “controlled release” has become associated with those systems from which therapeutic agents may be automatically delivered at pre defined rates over a long period of time. Products of this type have been formulated for oral, injectable and topical use and include inserts for placement in the body cavities as well.

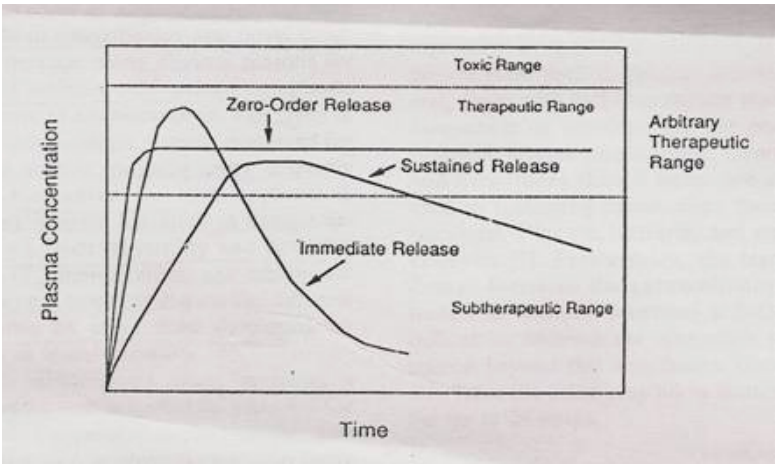


Fig no 1: Drug level verses time profile showing differences between zero order, controlled release, slow first order sustained release and release from conventional tablet.

In general, the main aim of sustained release dosage form is to maintain the therapeutic blood level or tissue level of the drug for an extended period of time. This is usually accomplished by attempting to obtain zero order release from the dosage form. Zero order release constitutes of the amount of drug in the delivery system (i.e.; a constant release rate). Sustained release systems generally don't attain this type of release and usually try to – zero order release by providing drug in a slow first order fashion (i.e.; concentration dependent).

1.1.1. Rationale of sustained drug delivery: [3, 4]

The basic rationale for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in selected route of administration. It is desirable that the duration of drug action become more to design properly. Rate controlled dosage form, and less, or not at all, a property of the drug molecules inherent kinetic properties.

As mentioned earlier, primary objectives of controlled drug delivery are to ensure safety and to improve efficiency of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and frequent dosing. For conventional dosage forms, only the dose (D) and dosing interval can vary and, for each drug, there exist a therapeutic window of plasma concentration, below which therapeutic effect is in sufficient, and above which toxic side effect are elicited. This is often defined as the ratio of median lethal dose (LD50) to median effective dose (ED50)

1.1.2. Modified – release delivery systems:

a. Delayed – release:

It is used repetitive, intermitting dosing of a drug from one or more immediate release units incorporated into single dosage form.

b. Sustained release:

It includes any drug delivery systems that achieve slow release of drug over an extended period of time. If the systems can provide some control, whether this be of a temporal or spatial nature, or both of drug release in the body.

c. Site specific targeting:

It refer to targeting of a drug directly to a certain biological location. In case site specific release, the target is adjacent or in the diseased organ or tissue.

d. Receptor targeting:

The target is the particular receptor for a drug within an organ or tissue.

Advantages of sustained drug delivery:

1. Avoid patient compliance problem.

a) Employ less amount drug

b) Minimize or eliminates local and systemic side effects.

c) Obtain less protestations or deduction in drug activity with chronic use.

d) Minimize drug accumulation with chronic dosing.

2. Improve efficacy in treatment.

a) Cure or controlled condition more promptly.

b) Improve control of condition i.e.; reduce fluctuation in drug level.

c) Improve bioavailability of some drugs.

d) Make use of special effects.

3. Economy.

Disadvantages of sustained release dosage forms:

a) Unpredictable and often poor *in-vitro* in vivo correlations, dose dumping, reduced potential for dosage adjustment and increased potential first pass clearance.

b) They are more costly.

c) Poor systemic availability in general.

d) Effective drug release time period is influenced and limited by GI residence time.

e) Need additional patient education.

f) Dugs having very short half.

1.1.3.Classification of oral sustained/controlled release systems: [5, 6]

A. **Continous release systems**

1. Dissolution controlled release systems

a) Matrix type b) Reservoir type

2. Diffusion controlled release systems

a) Matrix type b) Reservoir type

3. Dissolution and diffusion controlled release systems

4. Ion exchange resins drug complexes

5. Slow dissolving salts and complexes

6. pH dependent formulations

7. Osmotic pressure controlled systems

8.Hydrodynamic pressure controlled systems

B. Delayed transit and continuous release systems

1. Altered density systems

   I. High density

   II. Low density

   III. Floating

2. Mucoadhesive systems

3. Size based systems

C. **Delayed released systems**

1. Intestinal release systems

2. Colonic release systems

1.1.4. Factors Affecting Sustained Release Dosage Forms: [7, 8]

Factors governing the design of sustained /controlled release dosage forms.

A. Drug related factors

1. Aqueous solubility
2. Partition coefficient
3. Molecular size
4. Drug stability
5. Protein binding

B. Biological factors

1. Absorption
2. Distribution
3. Elimination
4. Duration of action

5. Margin of safety
6. Side effects
7. Disease state

1.2. METHODS:[9,10]

Granulation is the act or process of forming or crystallizing into grains. Granules typically have a size range between 0.2 to 4.0 mm depending on their subsequent use.

Synonym "Agglomeration": Agglomeration processes or in a more general term particle size enlargement technologies are great tools to modify product properties. Agglomeration of powders is widely used to improve physical properties like: wettability, flowability, bulk density and product appearance.

Granulation is carried out for various reasons, one of those is to prevent the segregation of the constituents of powder mix. Segregation is due to differences in the size or density of the component of the mix. Normally, the smaller and/or denser particles tend to concentrate at the base of the container with the larger and/or less dense ones on the top. An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule and segregation of granules will not occur.

Many powders, because of their small size, irregular shape or surface characteristics, are cohesive and do not flow well. Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties.

Some powders are difficult to compact even if a readily compactable adhesive is included in the mix, but granules of the same powders are often more easily compacted. This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granule.

For example, if one were to make tablets from granulated sugar versus powdered sugar, powdered sugar would be difficult to compress into a tablet and granulated sugar would be easy to compress. Powdered sugar's small particles have

poor flow and compression characteristics.These small particles would have to be compressed very slowly for a long period of time to make a worthwhile tablet. Unless the powdered sugar is granulated, it could not efficiently be made into a tablet that has good tablet characteristics such as uniform content or consistent hardness.

1.2.1. Granulation techniques

In pharmaceutical industry, two types of granulation technologies are employed, namely, Wet Granulation and Dry Granulation.

Wet Granulation

Wet granulation, the process of adding a liquid solution to powders, is one of the most common ways to granulate. It involves the massing of a mix of dry primary powder particles using a granulating fluid. The fluid contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic. Typical liquids include water, ethanol and isopropanol either alone or in combination. The liquid solution can be either aqueous based or solvent based. Aqueous solutions have the advantage of being safer to deal with than solvents.

Water mixed into the powders can form bonds between powder particles that are strong enough to lock them together. However, once the water dries, the powders may fall apart. Therefore, water may not be strong enough to create and hold a bond. In such instances, a liquid solution that includes a binder (pharmaceutical glue) is required. Povidone, which is a polyvinyl pyrrolidone (PVP), is one of the most commonly used pharmaceutical binders. PVP is dissolved in water or solvent and added to the process. When PVP and a solvent/water are mixed with powders, PVP forms a bond with the powders during the process, and the solvent/water evaporates (dries). Once the solvent/water has been dried and the powders have formed a more densely held mass, then the granulation is milled. This process results in the formation of granules.

The process can be very simple or very complex depending on the characteristics of the powders, the final objective of tablet making, and the equipment

that is available. In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which is subsequently dried.

1.3. TABLETS:[11,12]

Solid medicaments may be administered orally in the form of powders, pills, cachets, capsules or tablet. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug.

1.3.1. General properties of Tablet dosage forms:

1. A tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
2. Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
3. Should have the chemical and physical stability to maintain its physical attributes over time
4. The tablet must be able to release the medicinal agents in a predictable and reproducible manner.
5. Must have a chemical stability over time so as not to follow alteration of the medicinal agents.

1.3.2. BILAYER SUSTAINED RELEASE TABLETS: [13, 14]

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:

1. Drugs with short half-life require frequent administration, which increases the chances of missing dose of drug leading to poor patient compliance.
2. A typical peak-valley plasma concentration-time profile is obtained which makes difficult to attainment of steady state condition.

3. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{SS} values fall or rise beyond the therapeutic range.
4. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled and sustained drug delivery system. However despite of many advantages offered by oral sustained release dosage forms they have few disadvantages and **Lag time** is one of them. In order to achieve sustained therapeutic action oral SRDDS will release the drug at a slow rate and thus during the initial stages of medication, the plasma drug concentration generally stays below the minimum effective concentration and as a result the patient does not get any therapeutic benefit.

Bilayer SR tablets are a solution to above problem. These preparations provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific period of time. The major advantage of this category is that, in addition to the convenience of reduced frequency administration, it provides levels that are devoid of the peak and valley effect. Bilayer tablets are novel drug delivery systems where combinations of two or more drugs in a single unit having different release profiles which improves patient compliance, prolong the drug action, avoid saw tooth kinetics resulting in effective therapy along with better control of plasma drug levels.

Two layer tablets may be designed for sustained release-one for the immediate release of the drug and second layer for extended release thus maintaining prolonged blood level. Layers may be colour differently to identify the product the weight of each layer can be accurately controlled in contrast to putting one drug of a combination product in a sugar coating.

1.4. DISEASE PROFILE:[15]

1.4.1. REVIEW OF CONGESTIVE HEART FAILURE:

Congestive heart failure facts

- Congestive heart failure (CHF) is a condition in which the heart's function as a pump is inadequate to meet the body's needs.
- Many disease processes can impair the pumping efficiency of the heart to cause congestive heart failure.
- The symptoms of congestive heart failure vary, but can include fatigue, diminished exercise capacity, shortness of breath, and swelling.
- The diagnosis of congestive heart failure is based on knowledge of the individual's medical history, a careful physical examination, and selected laboratory tests.
- The treatment of congestive heart failure can include lifestyle modifications, addressing potentially reversible factors, medications, heart transplant, and mechanical therapies.
- The course of congestive heart failure in any given patient is extremely variable.

Congestive heart failure

Congestive heart failure (CHF) is a condition in which the heart's function as a pump is inadequate to deliver oxygen rich blood to the body. Congestive heart failure can be caused by:

1. diseases that weaken the heart muscle,
2. diseases that cause stiffening of the heart muscles, or
3. diseases that increase oxygen demand by the body tissue beyond the capability of the heart to deliver adequate oxygen-rich blood.

The heart has two atria (right atrium and left atrium) that make up the upper chambers of the heart, and two ventricles (left ventricle and right ventricle) that make up the lower chambers of the heart. The ventricles are muscular chambers that pump

blood when the muscles contract. The contraction of the ventricle muscles is called systole.

Many diseases can impair the pumping action of the ventricles. For example, the muscles of the ventricles can be weakened by heart attacks, infections (myocarditis) or toxins (alcohol, some chemotherapy agents). The diminished pumping ability of the ventricles due to muscle weakening is called systolic dysfunction. After each ventricular contraction (systole) the ventricle muscles need to relax to allow blood from the atria to fill the ventricles. This relaxation of the ventricles is called diastole.

Diseases such as hemochromatosis (iron overload) or amyloidosis can cause stiffening of the heart muscle and impair the ventricles' capacity to relax and fill; this is referred to as diastolic dysfunction. The most common cause of this is longstanding high blood pressure resulting in a thickened (hypertrophied) heart. Additionally, in some patients, although the pumping action and filling capacity of the heart may be normal, abnormally high oxygen demand by the body's tissues (for example, with hyperthyroidism or anemia) may make it difficult for the heart to supply an adequate blood flow (called high output heart failure).

In some individuals one or more of these factors can be present to cause congestive heart failure. The remainder of this article will focus primarily on congestive heart failure that is due to heart muscle weakness, systolic dysfunction.

Congestive heart failure can affect many organs of the body. For example:

- The weakened heart muscles may not be able to supply enough blood to the kidneys, which then begin to lose their normal ability to excrete salt (sodium) and water. This diminished kidney function can cause the body to retain more fluid.
- The lungs may become congested with fluid (pulmonary edema) and the person's ability to exercise is decreased.
- Fluid may likewise accumulate in the liver, thereby impairing its ability to rid the body of toxins and produce essential proteins.

- The intestines may become less efficient in absorbing nutrients and medicines.
- Fluid also may accumulate in the extremities, resulting in edema (swelling) of the ankles and feet.

Eventually, untreated, worsening congestive heart failure will affect virtually every organ in the body.

Causes of congestive heart failure

Many disease processes can impair the pumping efficiency of the heart to cause congestive heart failure. In the United States, the most common causes of congestive heart failure are:

- coronary artery disease
- high blood pressure (hypertension)
- longstanding alcohol abuse
- disorders of the heart valves

unknown (idiopathic) causes, such as after recovery from myocarditis

Less common causes include viral infections of the stiffening of the heart muscle, thyroid disorders, disorders of the heart rhythm, and many others.

It should also be noted that in patients with underlying heart disease, taking certain medications can lead to the development or worsening of congestive heart failure. This is especially true for those drugs that can cause sodium retention or affect the power of the heart muscle. Examples of such medications are the commonly used nonsteroidal anti-inflammatory drugs (NSAIDs), which include ibuprofen (Motrin and others) and naproxen (Aleve and others) as well as certain steroids, some medication for diabetes (such as rosiglitazone [Avandia] or pioglitazone [Actos]), and some calcium channel blockers.

Symptoms of congestive heart failure

The symptoms of congestive heart failure vary among individuals according to the particular organ systems involved and depending on the degree to which the rest of the body has "compensated" for the heart muscle weakness.

An early symptom of congestive heart failure is fatigue. While fatigue is a sensitive indicator of possible underlying congestive heart failure, it is obviously a nonspecific symptom that may be caused by many other conditions. The person's ability to exercise may also diminish. Patients may not even sense this decrease and they may subconsciously reduce their activities to accommodate this limitation.

As the body becomes overloaded with fluid from congestive heart failure, swelling (edema) of the ankles and legs or abdomen may be noticed. This can be referred to as "right sided heart failure" as failure of the right sided heart chambers to pump venous blood to the lungs to acquire oxygen results in buildup of this fluid in gravity-dependent areas such as in the legs. The most common cause of this is longstanding failure of the left heart, which may lead to secondary failure of the right heart. Right-sided heart failure can also be caused by severe lung disease (referred to as "cor pulmonale"), or by intrinsic disease of the right heart muscle (less common)

In addition, fluid may accumulate in the lungs, thereby causing shortness of breath, particularly during exercise and when lying flat. In some instances, patients are awakened at night, gasping for air.

Some may be unable to sleep unless sitting upright.

The extra fluid in the body may cause increased urination, particularly at night.

Accumulation of fluid in the liver and intestines may cause nausea, abdominal pain, and decreased appetite.

Congestive heart failure diagnosed

The diagnosis of congestive heart failure is most often a clinical one that is based on knowledge of the patient's pertinent medical history, a careful physical examination, and selected laboratory tests.

A thorough patient history may disclose the presence of one or more of the symptoms of congestive heart failure described above. In addition, a history of significant coronary artery disease, prior heart attack, hypertension, diabetes, or significant alcohol use can be clues.

The physical examination is focused on detecting the presence of extra fluid in the body (breath sounds, leg swelling, or neck veins) as well as carefully characterizing the condition of the heart (pulse, heart size, heart sounds, and murmurs).

Useful diagnostic tests include the electrocardiogram (ECG) and chest X-ray to detect previous heart attacks, arrhythmia, heart enlargement, and fluid in and around the lungs. Perhaps the single most useful diagnostic test is the echocardiogram, in which ultrasound is used to image the heart muscle, valve structures, and blood flow patterns. The echocardiogram is very helpful in diagnosing heart muscle weakness. In addition, the test can suggest possible causes for the heart muscle weakness (for example, prior heart attack, and severe valve abnormalities). Virtually all patients in whom the diagnosis of congestive heart failure is suspected should ideally undergo echocardiography early in their assessment.

Nuclear medicine studies assess the overall pumping capability of the heart and examine the possibility of inadequate blood flow to the heart muscle. Heart catheterization allows the arteries to the heart to be visualized with angiography (using dye inside of the blood vessels that can be seen using X-ray methods). During catheterization the pressures in and around the heart can be measured and the heart's performance assessed. In rare cases, a biopsy of the heart tissue may be recommended to diagnose specific diseases. This biopsy can often be accomplished through the use of a special catheter device that is inserted into a vein and maneuvered into the right side of the heart.

Another helpful diagnostic test is a blood test called a BNP or B-type natriuretic peptide level. This level can vary with age and gender but is typically elevated from heart failure and can aid in the diagnosis, and can be useful in following the response to treatment of congestive heart failure.

The choice of tests depends on each patient's case and is based on the suspected diagnoses.

Treatment of congestive heart failure

Lifestyle modifications

After congestive heart failure is diagnosed, treatment should be started immediately. Perhaps the most important and yet most neglected aspect of treatment involves lifestyle modifications. Sodium causes an increase in fluid accumulation in the body's tissues. Because the body is often congested with excess fluid, patients become very sensitive to the levels of intake of sodium and water. Restricting salt and fluid intake is often recommended because of the tendency of fluid to accumulate in the lungs and surrounding tissues. An American "no added salt" diet can still contain 4 to 6 grams (4000 to 6000 milligrams) of sodium per day. In individuals with congestive heart failure, an intake of no more than 2 grams (2000 milligrams) of sodium per day is generally advised. Reading food labels and paying close attention to total sodium intake is very important. Severe restriction of alcohol consumption also is advised.

Likewise, the total amount of fluid consumed must be regulated. Although many people with congestive heart failure take diuretics to aid in the elimination of excess fluid, the action of these medications can be overwhelmed by an excess intake of water and other fluids. The maxim that "drinking eight glasses of water a day is healthy" certainly does not apply to patients with congestive heart failure. In fact, patients with more advanced cases of congestive heart failure are often advised to limit their total daily fluid intake from all sources to 2 quarts. The above guidelines for sodium and fluid intake may vary depending on the severity of congestive heart failure in any given individual and should be discussed with their physician.

An important tool for monitoring an appropriate fluid balance is the frequent measurement of body weight. An early sign of fluid accumulation is an increase in body weight. This may occur even before shortness of breath or swelling in the legs and other body tissues (edema) is detected. A weight gain of two to three pounds over two to three days should prompt a call to the physician, who may order an increase in the dose of diuretics or other methods designed to stop the early stages of fluid accumulation before it becomes more severe.

Aerobic exercise, once discouraged for congestive heart failure patients, has been shown to be beneficial in maintaining overall functional capacity, quality of life, and perhaps even improving survival. Each person's body has its own unique ability to compensate for the failing heart. Given the same degree of heart muscle weakness, individuals may display widely varying degrees of limitation of function. Regular exercise, when tailored to the person's tolerance level, appears to provide significant benefits and should be used only when the individual is compensated and stable.

1.4.2. REVIEW OF HYPERTENSION:[16]

Hypertension (HTN) or **High Blood Pressure** is a cardiac chronic medical condition in which the systemic arterial blood pressure is elevated. It is the opposite of hypotension. Hypertension is classified as either primary (essential) hypertension or secondary hypertension; About 90–95% of cases are categorized as "primary hypertension," which means high blood pressure with no obvious medical cause. The remaining 5–10% of cases (Secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart or endocrine system.

Persistent hypertension is one of the risk factors for stroke, myocardial infarction, heart failure and arterial aneurysm, and is a leading cause of chronic kidney failure. Moderate elevation of arterial blood pressure leads to shortened life expectancy. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications, although drug treatment may prove necessary in patients for whom lifestyle changes prove ineffective or insufficient.

Classification

The variation in pressure in the left ventricle (blue line) and the aorta (red line) over two cardiac cycles ("heart beats"), showing the definitions of systolic and diastolic pressure.

Classification	Systolic pressure		Diastolic pressure	
	mmHg	**kPa**	**mmHg**	**kPa**
Normal	90–119	12–15.9	60–79	8.0–10.5
Prehypertension	120–139	16.0–18.5	80–89	10.7–11.9
Stage 1	140–159	18.7–21.2	90–99	12.0–13.2
Stage 2	≥160	≥21.3	≥100	≥13.3
Isolated systolic hypertension	≥140	≥18.7	<90	<12.0

Blood pressure is usually classified based on the systolic and diastolic blood pressures. Systolic blood pressure is the blood pressure in vessels during a heart beat. Diastolic blood pressure is the pressure between heartbeats. A systolic or the diastolic blood pressure measurement higher than the accepted normal values for the age of the individual is classified as prehypertension or hypertension.

Hypertension has several sub-classifications, including hypertension stage I, hypertension stage II, and isolated systolic hypertension. Isolated systolic hypertension refers to elevated systolic pressure with normal diastolic pressure and is common in the elderly. These classifications are made after averaging a patient's resting blood pressure readings taken on two or more office visits. Individuals older than 50 years are classified as having hypertension if their blood pressure is consistently at least 140 mmHg systolic or 90 mmHg diastolic. Patients with blood pressures higher than 130/80 mmHg with concomitant presence of diabetes mellitus or kidney disease require further treatment.

Hypertension is also classified as resistant if medications do not reduce blood pressure to normal levels.

Exercise hypertension is an excessively high elevation in blood pressure during exercise. The range considered normal for systolic values during exercise is individual is at risk for developing hypertension at rest.

Signs and Symptoms

Mild to moderate essential hypertension is usually asymptomatic.

Accelerated Hypertension

Accelerated hypertension is associated with headache, drowsiness, confusion, vision disorders, nausea, and vomiting. These symptoms are collectively called hypertensive encephalopathy. Hypertensive encephalopathy is caused by severe small blood vessel congestion and brain swelling, which is reversible if blood pressure is lowered.

Secondary Hypertension

Some additional signs and symptoms suggest that the hypertension is caused by disorders in hormone regulation. Hypertension combined with obesity distributed on the trunk of the body, accumulated fat on the back of the neck ('buffalo hump'), wide purple marks on the abdomen (abdominal striae), or the recent onset of diabetes suggests that an individual has a hormone disorder known as Cushing's syndrome. Hypertension caused by other hormone disorders such as hyperthyroidism, hypothyroidism, or growth hormone excess will be accompanied by additional symptoms specific to these disorders. For example, hyperthyrodism can cause weight loss, tremors, heart rate abnormalities, reddening of the palms, and increased sweating. Signs and symptoms associated with growth hormone excess include coarsening of facial features, protrusion of the lower jaw, enlargement of the tongue, excessive hair growth, darkening of the skin color, and excessive sweating. Other hormone disorders like hyperaldosteronism may cause less specific symptoms such as numbness, excessive urination, excessive sweating, electrolyte imbalances and dehydration, and elevated blood alkalinity. and also cause mental pressure.

In pregnancy

Hypertension in pregnant women is one symptom of pre-eclampsia. Pre-eclampsia can progress to a life-threatening condition called eclampsia, which is the development of protein in the urine, generalized swelling, and severe seizures. Other symptoms indicating that brain function is becoming impaired may precede these seizures such as nausea, vomiting, headaches, and vision loss.

In addition, the systemic vascular resistance and blood pressure decrease during pregnancy. The body must compensate by increasing cardiac output and blood volume to provide sufficient circulation in the utero-placental arterial bed.

In Children

Some signs and symptoms are especially important in newborns and infants such as failure to thrive, seizures, irritability, lack of energy, and difficulty breathing. In children, hypertension can cause headache, fatigue, blurred vision, nosebleeds, and facial paralysis.

Even with the above clinical symptoms, the true incidence of pediatric hypertension is not known. In adults, hypertension has been defined due to the adverse effects caused by hypertension. However, in children, similar studies have not been performed thoroughly to link any adverse effects with the increase in blood pressure. Therefore, the prevalence of pediatric hypertension remains unknown due to the lack of scientific knowledge.

CAUSE

Essential Hypertension

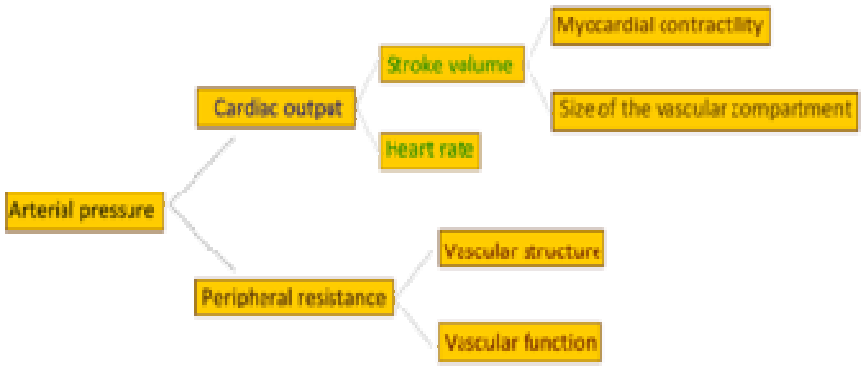
Essential hypertension is the most prevalent hypertension type, affecting 90–95% of hypertensive patients. Although no direct cause has been identified, there are many factors such as sedentary lifestyle, smoking, stress, visceral obesity, potassium deficiency (hypokalemia), obesity (more than 85% of cases occur in those with a body

mass index greater than 25), salt (sodium) sensitivity, alcohol intake, and vitamin D deficiency that increase the risk of developing hypertension. Risk also increases with aging, some inherited genetic mutations, and having a family history of hypertension. An elevated level of renin, a hormone secreted by the kidney, is another risk factor, as is sympathetic nervous system overactivity. Insulin resistance, which is a component of syndrome X (or the metabolic syndrome), is also thought to contribute to hypertension. Recent studies have implicated low birth weight as a risk factor for adult essential hypertension.

Secondary Hypertension

Secondary hypertension by definition results from an identifiable cause. This type is important to recognize since it's treated differently to essential hypertension, by treating the underlying cause of the elevated blood pressure. Hypertension results in the compromise or imbalance of the pathophysiological mechanisms, such as the hormone-regulating endocrine system, that regulate blood plasma volume and heart function. Many conditions cause hypertension. Some are common, well-recognized secondary causes such as renovascular hypertension and Cushing's syndrome, which is a condition where the adrenal glands overproduce the hormone cortisol. Hypertension is also caused by other conditions that cause hormone changes, such as hyperthyroidism, hypothyroidism (citation needed), and certain tumors of the adrenal medulla (e.g., pheochromocytoma). Other common causes of secondary hypertension include kidney disease, obesity/metabolic disorder, pre-eclampsia during pregnancy, the congenital defect known as coarctation of the aorta, and certain prescription and illegal drugs.

Pathophysiology



A diagram explaining factors affecting arterial pressure

Most of the mechanisms associated with secondary hypertension are generally fully understood. However, those associated with essential (primary) hypertension are far less understood. What is known is that cardiac output is raised early in the disease course, with total peripheral resistance (TPR) normal; over time cardiac output drops to normal levels but TPR is increased. Three theories have been proposed to explain this:

- Inability of the kidneys to excrete sodium, resulting in natriuretic factors such as Atrial Natriuretic Factor being secreted to promote salt excretion with the side effect of raising total peripheral resistance.
- An overactive Renin-angiotensin system leads to vasoconstriction and retention of sodium and water. The increase in blood volume plus vasoconstriction leads to hypertension.
- An overactive sympathetic nervous system, leading to increased stress responses.

It is also known that hypertension is highly heritable and polygenic (caused by more than one gene) and a few candidate genes have been postulated in the etiology of this condition.

Recently, work related to the association between essential hypertension and sustained endothelial damage has gained popularity among hypertension scientists. It remains unclear, however, whether endothelial changes precede the development of hypertension or whether such changes are mainly due to longstanding elevated blood pressures.

Diagnosis

Hypertension is generally diagnosed on the basis of a persistently high blood pressure. Usually this requires three separate sphygmomanometer measurements at least one week apart. Diagnosis often entails three separate visits to the physician's office. Initial assessment of the hypertensive patient should include a complete history and physical examination. Exceptionally, if the elevation is extreme, or if symptoms of organ damage are present, then a diagnosis may be made and treatment started immediately.

Once the diagnosis of hypertension has been made, physicians will attempt to identify the underlying cause based on risk factors and other symptoms, if present. Secondary hypertension is more common in preadolescent children, with most cases caused by renal disease. Primary or essential hypertension is more common in adolescents and has multiple risk factors, including obesity and a family history of hypertension. Laboratory tests can also be performed to identify possible causes of secondary hypertension, and to determine whether hypertension has caused damage to the heart, eyes, and kidneys. Additional tests for diabetes and high cholesterol levels are usually performed because these conditions are additional risk factors for the development of heart disease and require treatment.

Prevention

The degree to which hypertension can be prevented depends on a number of features including current blood pressure level, sodium/potassium balance, detection and omission of environmental toxins, changes in end/target organs (retina, kidney, heart, among others), risk factors for cardiovascular diseases and the age at diagnosis of prehypertension or at risk for hypertension. A prolonged assessment that involves repeated blood pressure measurements provides the most accurate blood pressure level assessment. Following this, lifestyle changes are recommended to lower blood pressure, before the initiation of prescription drug therapy. The process of managing prehypertension according the guidelines of the British Hypertension Society suggest the following lifestyle changes:

- Weight reduction and regular aerobic exercise (e.g., walking): Regular exercise improves blood flow and helps to reduce the resting heart rate and blood pressure.
- Reduce dietary sugar
- Reduce sodium (salt) in the body by disuse of condiment sodium and the adoption of a high potassium diet which rids the renal system of excess sodium. Many people use potassium chloride salt substitute to reduce their salt intake.

Additional dietary changes beneficial to reducing blood pressure include the DASH diet (**d**ietary **a**pproaches to **s**top **h**ypertension) which is rich in fruits and vegetables and low-fat or fat-free dairy products. Research sponsored by the National Heart, Lung, and Blood Institute. showed this diet to be effective. In addition, an increase in dietary potassium, which offsets the effect of sodium has been shown highly effective in reducing blood pressure.

Discontinuing tobacco use and alcohol consumption has been shown to lower blood pressure. The exact mechanisms are not fully understood, but blood pressure (especially systolic) always transiently increases following alcohol or nicotine consumption. Abstaining from cigarette smoking reduces the risks of stroke and heart attack associated with hypertension.

Vasodialators such as niacin.

Limiting alcohol intake to less than 2 standard drinks per day can reduce systolic blood pressure by between 2-4mmHg.

Reducing stress, for example with relaxation therapy, such as meditation and other mindbody relaxation techniques,by reducing environmental stress such as high sound levels and over-illumination can also lower blood pressure. Jacobson's Progressive Muscle Relaxation and biofeedback are also beneficial, such as device-guided paced breathing,although meta-analysis suggests it is not effective unless combined with other relaxation techniques.

Increasing omega 3 fatty acids can help lower hypertension. Fish oil is shown to lower blood pressure in hypertensive individuals. The fish oil may increase sodium and water excretion.

2.LITERATURE REVIEW

Sonia Pandey *et al*, (2010) Carvedilol was formulated as a bilayered buccal tablet in order to avoid the first-pass effect and decrease the drug loss using different polymers and excipients. Eight formulations were made using different ratio of carbopol 934P and HPMC K4M.The formulations were tested for *in vitro* drug release, *in vitro* bioadhesion, moisture absorption and in vitro drug permeation through porcine buccal mucosa. The dissolution of Carvedilol from all the prepared tablets into phosphate buffer (pH 6.8) was controlled and followed by non-fickian release mechanism. Dissolution studies of the tablets of optimized batch containing 5% Carbopol 934P/65% HPMC K4M/30% lactose showed 82.7% release of drug in 6 h. The mucoadhesive strength and residence time of the optimized batch are 17.93 g and 9.45 h respectively. The swelling index and microenvironment pH of the optimized batch after 6 h are 77.54 and 6.76 respectively. Procured sample of carvedilol was tested for its identification by taking FTIR of pure drug. Drug excipient compatibility was done at 30°C ,65% ± 5%RH, and 40°C 75% ± 5%RH using open and closed vial for four weeks and observed for physical changes.

Ziyaur Rahman *et al, (*2006) Investigated was to develop a bilayer floating tablet (BFT) for captopril using direct compression technology. HPMC K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934p, alone or in combination with the drug. The floating behaviour and *in vitro* dissolution studies were carried out in a USP 23 apparatus 2 in simulated gastric fluid (without enzyme, pH 1.2). Final formulation released approximately 95% drug in 24 h *in vitro*, while the floating lag time was 10 min and the tablet remained floatable throughout all studies. Final formulation followed the Higuchi release model and showed no significant change in physical appearance, drug content, floatability or in vitro dissolution pattern after storage at 45 °C/75% RH for three months.

Swamy P.V. *et al,* (2011) Design and evaluate bilayer buccal tablets of granisetron hydrochloride (an anti-emetic drug), in order to overcome bioavailability problems, to reduce dose dependent side effects and frequency of administration. Bilayer buccal tablets containing the drug were prepared by direct compression method using

combination of polymers (such as sodium alginate, HPMC 50 cps and Carbopol 934p) and ethyl cellulose as an impermeable backing layer to release the drug in a unidirectional way toward the mucosa, thus avoiding loss of drug due to wash out by saliva. The designed tablets were evaluated for various physical and biological parameters, drug content uniformity, *in-vitro* drug release, short-term stability, drug-excipient interactions (FTIR). The formulation SAF with the drug matrix layer 1 composition- sodium alginate (47% w/w), Carbopol 934p (3% w/w), PVP K-30 (binder, 30% w/w) and mannitol (channeling agent, 15% w/w) was found to be promising. This optimized formulation exhibited an *in vitro* drug release of 94% in 8 h along with satisfactory bioadhesion strength (4.6 gm).Short-term stability studies (40±2 C/75±5% RH for 3 months)

N.G.Raghavendra Rao *et al*, (2010) Develop controlled zero-order release glipizide bilayered matrix tablets using different grades of hydroxy propyl methyl cellulose (HPMC) as novel release modifier along with xanthan gum (XG), guar gum (GG), and karaya gum (KG) as release retardants. Bilayered matrix tablets of glipizide were prepared by wet granulation method. The release rate were modulated by varying concentration of different types of rate controlling material as well as in a combination of two different rate controlling material. After evaluation of physical properties of tablets, the *in vitro* release study was performed in phosphate buffer pH 7.4 upto 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. All precompressional parameters were found to be within acceptable standard limits. It was observed that bilayer matrix tablets contained polymer blend of HPMC/Ethyl cellulose were successfully sustained the release of drug upto 12 hrs. The release data were fit into

different kinetic models (zero order, first order and Korsemeyer-Peppas powers law equation). The DSC and FTIR studies demonstrated that there was no interaction between polymers and drug. Stability studies were carried out according ICH guidelines. Stability studies (40±2oC/75±5% RH) for 6 months indicated that glipizide was stable in matrix tablets.

N.N.Rajendran *et al*, (2011) Establish Bi-layer tablets containing Metformin HCl as sustained release and Pioglitazone HCl as immediate release layer.Sustained layer were prepared by wet granulation method using different viscosity grade of HPMC (HPMC K4M & HPMC K100M) as polymers and immediate release layer were prepared by direct compression method using superdisintegrants such as sodium starch glycolate and crosscarmellose sodium. The tablets were evaluated for physicochemical properties. All the values were found to be within limit. In vitro release studies were carried out by USP type-2 paddle apparatus. The result showed that combinations of polymers namely HPMC K100M and HPMC K4M in sustained layer can control the release of drug. The *in vitro* release profiles of drug from sustained release layer could be best expressed by Higuchi's equation as the plots showed high linearity (R2 >0.988) and diffusion was the dominant mechanism of drug release. The formulations (P6M7) having immediate release layer produces immediate effect within 54 second followed by sustained release (97.35%) at 8 hrs and it comparable with innovator.

Anilkumar J. Shinde *et al*, (2010) Investigation was to prepared a gastroretentive floating drug delivery system (GFDDS) of cephalexin(CFL). Sustained release of floating tablets of cephalexin were formulated employing the hydrophilic polymer hydroxy propyl methyl cellulose (HPMC), gas generating agent sodium bicarbonate and citric acid. A 32 factorial design was applied systematically; the amount of citric acid (X1) and amount of HPMC K100M (X2) were selected as independent variables. The time required for 50% drug release (t50%), percentage drug release at 12 hours (Q12) and percentage drug release at 6 hours (Q6) were selected as dependent variables. The results of factorial design indicated that high level of HPMC K100M and citric acid favors preparation of floating sustained release tablet of cephalexin. The granules were prepared by wet granulation method and evaluated for their granules properties.

R.Nagaraju *et al*, (2009) Salbutamol and theophylline are available in conventional dosage forms, administered four times a day,leading to saw tooth kinetics and resulting in ineffective therapy. The combination of these two drugs in a single dosage

form will enhance the patient compliance and prolong bronchodilation. Various polymers, such as hydroxy propyl methylcellulose K4M (HPMC- K4M), hydroxy propyl methylcellulose K100M (HPMC- K100M), xanthan gum, ethyl cellulose and hydroxy propyl methylcellulose phthalate (HPMC-P) were studied. HPMC-P and HPMC- K4M were found to be best in controlling the release. *In-vitro* dissolution studies were carried out for all the bi-layered tablets developed using USP dissolution apparatus type 2 (paddle). It was found that the tablet FB15-FW3 showed 50% release of salbutamol in first hour and the remaining was released for eight hours. However, theophylline was found to be released as per the USP specifications. The IR spectrum was taken for FB15-FW3 formulation and it revealed that there is no disturbance in the principal peaks of pure drugs salbutamol and theophylline.

B.Vijaya Kumar *et al*, (2010) Develop a Bilayer tablet of guaifenesin (GBT) using superdisintegrant MCC and sodium starch glycolate for the fast release layer and metalose 90 SH and carbopol 934 for the sustaining layer. *In vitro* dissolution studies were carried out in a USP 24 apparatus I. The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. *In vitro* dissolution kinetics followed the Higuchi model via a non-Fickian diffusion controlled release mechanism after the initial burst release. Stability studies conducted for optimized formulation did not show any change in physical appearance, drug content, matrix integrity and in vitro drug release.

Chinam Niranjan Patra *et al*, (2007) Develop a bilayer tablet of propranolol hydrochloride using superdisintegrant sodium starch glycolate for the fast release layer and water immiscible polymers such as ethylcellulose, Eudragit RLPO and Eudragit RSPO for the sustaining layer. *In vitro* dissolution studies were carried out in a USP 24 apparatus I. The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. *In vitro* dissolution kinetics followed the Higuchi model via a non-Fickian diffusion controlledrelease mechanism after the initial burst release. FT-IR studies revealed that there was no interaction between the drug and polymers used in the study. Statistical analysis (ANOVA) showed no significant

difference in the cumulative amount of drug release after 15 min, but significant difference ($p < 0.05$) in the amount of drug released after 12 h from optimized formulations was observed.

SH Lakade *et al*, (2008) Develop hydrophilic polymer (HPMC) and hydrophobic polymer (Ethyl cellulose) based Nicorandil matrix sustained release tablet which can release the drug up to time of 24 hrs in predetermined rate. The formulation of Nicorandil matrix tablet was prepared by the polymer combination in order to get required theoretical release profile. The influence of hydrophilic and hydrophobic polymer and granulation technique on Nicorandil was studied. The formulated tablet were also characterized by physical and chemical parameters, The *in-vitro* release rate profile should the higher concentration of F2 polymer in tablet, the combination of hydrophilic and hydrophobic combination showed less result than use of alone. The *in–vitro* release data was well fit to Peppas and Hixon crowel release kinetics.

MR.Ashish A Pahade *et al*, (2010) Develop bilayer sustained release tablet of Isosorbide mononitrate, an anti-anginal organic nitrate vasodilator. The tablets were prepared by wet granulation method. Hydrophilic and hydrophobic matrix materials such as hydroxypropyl methylcellulose, and polyox were used, which can release the drug up to 24hrs in predetermined rate. Binder used was pvp k-30. The influence of hydrophilic and hydrophobic polymer and granulation technique was studied.

P.Dinesh Kumar *et al*, (2010) Prepare a bilayer gastro retentive tablet of ranitidine using direct compression technology and optimize the type and concentration of polymer to give maximum retentive effect with good drug release profile. Ranitidine H_2 receptor antagonist having short biological half life (2-3.5 h), absorption in the initial part of the small intestine and 50% absolute bioavailability of drug favor development of sustained release floating formulation. In this study, a bilayer tablet was prepared which contains an immediate release portion and a floating layer. HPMC-K-100, HPMC-K-4M, HPMC-E-15, CARBOPOL-934 were used as gel forming agents either alone or in combination. Sodium bicarbonate, and citric acid as gas generating agent, lactose as additive combine with the polymer to form the

floating layer[1]. The bilayer tablets were characterized by lag time, floating time, weight variation, drug content and dissolution profile. Best Formulation BLF6 [HPMC-K100 (1:1)] shows lag time of 25 s, floating time of 24 h and drug release of 99.85%. The best formulation was taken up for animal studies as approved by Institutional Animal Ethical Committee. The X-ray studies for floating properties of tablet and the *in vivo* bioavailability studies for the formulation was carried out using rabbits which showed a significant increase in bioavailability of drug as compared with conventional dosage forms. The optimized formulation was subjected to stability studies at 40 ± 2^{0} and 75 ± 5% RH for period of three months.

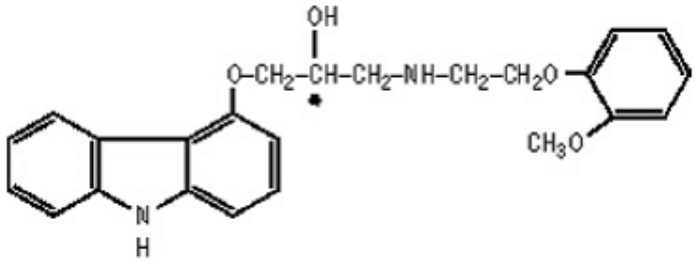
3.DRUG PROFILE

Carvedilol:[17]

Description **:** It is a non – selective beta blocker; it blocks β-1 and β-2 adrenergic receptors as well as the α-1 adrenergic receptors. It is a white or almost white, crystalline powder.

Chemical Name **:** (2RS)-1-(9 H-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy) ethyl] amino]propan-2-ol

Chemical Structure:



Molecular Formula : $C_{24}H_{26}N_2O_4$

Molecular Weight : 406.5 g/mole

Melting point : 114 - 115^{0}C.

Solubility : It is easily soluble in dimethyl sulfoxide (DMSO), also easily soluble in methanol and methelene chloride, isopropranolol, ethyl ether and ethanol can partially dissolve. Practically insoluble in water.

Dose : 25mg twice a day in the treatment of congestive heart failure.

Elimination half life **:** 6 - 8 hours

Bioavailability **:** 25 - 35%

3.1.PHRMACOKINETICS:[18]

Absorption

i.) Non-genetic

a. Food: decreases rate (not extent) of absorption

b. Age: 50% increase in bioavailability in elderly (increased plasma concentrations)

c. Liver disease: oral bioavailability significantly increased

d. Concomitant medications/substances: p-glycoprotein inhibitors

ii.) Genetic

a. Genetic variation in p-glycoprotein gene

Distribution

i.) Non-genetic

a. Liver disease: 4-fold increase in volume of distribution

b. Altered serum protein (>95% protein bound, primarily to albumin)

c. Concomitant medications/substances: p-glycoprotein inhibitors or activators

ii.) Genetic

a. Genetic variation in p-glycoprotein gene

Metabolism

I) Non-genetic

a. Congestive heart failure (CHF): 30-40% higher plasma concentrations

b. Liver impairment

i. 4- to 7-fold higher concentrations in cirrhotic liver disease

ii. Contraindicated in severe hepatic impairment

c. Concomitant medications/substances: CYP2C9**,** CYP2D6**,** CYP3A4, CYP2C19, CYP1A2, CYP2E1inducers or inhibitors

II) Genetic

a. Genetic variation in drug metabolizing enzyme gene(s): CYP2C9**,** CYP2D6**,** CYP3A4, CYP2C19, CYP1A2, CYP2E1

Excretion

i.) Non-genetic

a.Renal impairment: increased plasma concentrations

b. Renal impairment + hypertension: markedly increased plasma concentrations

c. 50% shorter elimination half-life in pediatrics (ages 6 weeks – 19 years) with CHF

d. Age: Elimination half-life increases with age in pediatrics

ii.) Genetic

a. No clear genetic factors affecting excretion.

3.2. PHRMACODYNAMICS:

Receptors

i.) Non-genetic

a. Concomitant medications: alpha- or beta-adrenergic receptor agonists/antagonists (may block or enhance therapeutic effects of carvedilol)

ii.) Genetic

a. Genetic variation in beta-1 adrenergic receptor gene

b. Genetic variation in alpha-1 adrenergic receptor gene

c. Genetic variation in Gs protein alpha subunit gene

Transporters

i.) Non-genetic

Concomitant medications/substances: p-glycoprotein inhibitors or activators.

ii.) Genetic

Genetic variation in p-glycoprotein gene.

3.3. SIDE EFFECTS AND PRECAUTIONS:

Dizziness, Edema (fluid accumulation), decreased heart rate, diarrhea, postural hypotension, irregular heart rhythm, abnormalities of vision.

Carvedilol should be used cautiously in patients who use diuretics or who are elderly or have cirrohosis, asthma, peripheral vascular disease, hyperthyroidism, variant angina and kidney disease.

3.4. CONTRAINDICATIONS:

It is contraindicated during pregnancy.

4. POLYMER PROFILE

4.1. ETHYLCELLULOSE: [19, 20]

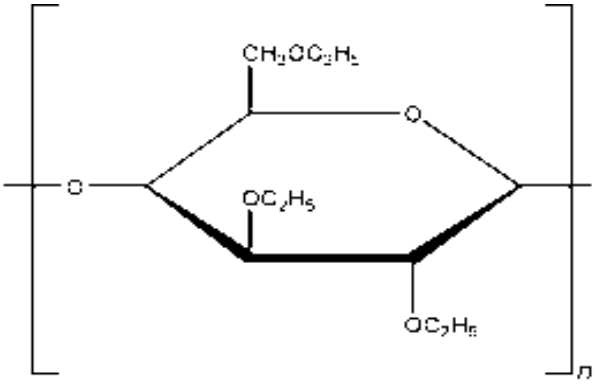
Description:

Ethyl cellulose is a tasteless, free-flowing, white to light tan colored powder.

Chemical Name:

Cellulose ethyl ether.

Chemical Structure:



Functional Category :

Coating agent, flavoring fixative, tablet binder, tablet filler.

Viscosity :

increasing agent.

Solubility:

Soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene. Practically insoluble in glycerin, propylene glycol and water.

Bulk density : 0.4 g/cm^3

Viscosity : 7 to 100 mPa s for 5% w/v solutions

Specific gravity : 1.12–1.15 g/cm^3

Stability:

Ethyl cellulose is a stable, slightly hygroscopic material chemically resistant to alkalis (both dilute and concentrated) and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.

Incompatibility:

Incompatible with paraffin wax and microcrystalline wax.

Application:

1) The main use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules.

2) Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethyl cellulose to inhibit oxidation.

3) Modified-release tablet formulations may also be produced using ethyl cellulose as a matrix former

Safety:

Ethyl cellulose is widely used in oral and topical Pharmaceutical formulations. It is also used in food products.

4.2. EUDRAGIT RSPO: [21]

Synonyms:

Polymeric methacrylates.

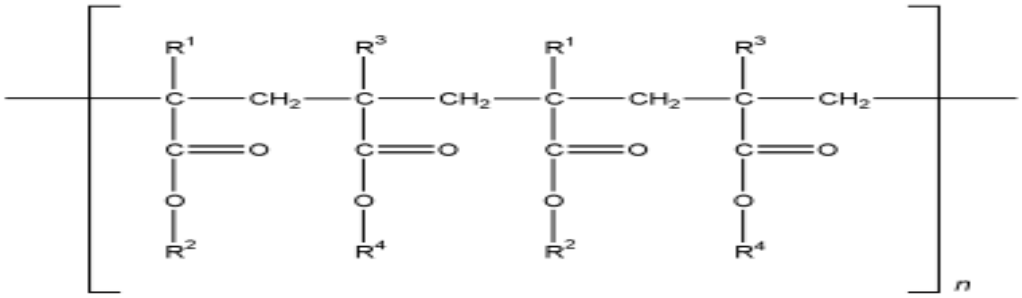
Description:

Fine white powder with slightly amine-like odor.

Chemical Name:

Poly (ethylacrylate,methyl methacrylate) trimethyl ammonio ethyl methacrylate chloride.

Chemical Structure:



Functional category : Film former, Tablet binders, Tablet diluents, sustained release polymer.

Behavior in Digestive Juices : Insoluble film of low permeability.

Bulk Density : 0.390 g/cm^3

True Density : 0.816 - 0.836 g/cm^3

Marketed forms : Powder

Flash point : Not inflammable.

Solubility:

Soluble in acetone, alcohol, dichloromethane, ethyl acetate, insoluble in water and petroleum ether.

Stability and Storage:

Dry powder polymer forms are stable at temperatures less than 30°C and should be stored in a tightly closed container at less than 30°C.

Applications :

Eudragit is employed as a coating material, usually for coating pellets or micro particles that are filled in to capsules or compressed into tablets. Eudragit RS has been used as a sustained release coating material. Water can penetrate in the Eudragit RS material and dissolve the encapsulated material, which then diffuses in the aqueous phase and finally into bulk solution. Eudragit serves as a matrix in which the active is embedded. The matrix structure is obtained by direct compression and wet granulation. Eudragit may additionally be used to form the matrix layers of transdermal delivery system. They have also been used to prepare novel gel formulation for rectal administration.

4.3. HYDROXY PROPYL METHYL CELLULOSE 4000: [22]

Non Proprietary Name:

BP **:** Hypermellose

PhEur **:** Methylhydroxypropylcellulosum

USP **:** Hydroxypropyl methyl cellulose

Synonyms:

Cellulose, hydroxypropyl methyl ether, methocel, ethylcellulose propylene glycol ether, methyl hydroxyl propylcellulo metolose, pharmacoat.

Description:

Hydroxypropyl methylcellulose is an odourless and tasteless white or creamy white coloured fibrous or granular powder.

Chemical Name:

Cellulose, 2-Hydroxypropyl methyl ether.

Functional Category:

Coating agent, film former, stabilizing agent, suspending agent, tablet binder, viscosity increasing agent.

Empirical Formula:

The Ph Eur describes HPMC as a partly O-methylated and o-(2-hydroxypropylated) cellulose. It is available in several grades which vary in viscosity and extent of substitution. HPMC defined in the USP XXII specifies the substitution type by appending a four digit number to the non proprietary name, e.g., hydroxypropyl methylcellulose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydropropoxy group ($OCH_2CHOHCH_3$).

Tapped Density **:** 0.05-0.70g/cm^3 for pharmacoat.

Melting Point **:** Browns at 190-200^{0}C, chars at 225-230^{0}C.

Solubility:

Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane.

Stability and Storage:

HPMC is a stable material although it is hygroscopic after drying. Solutions are stable between pH 3-11. Increasing temperature reduces the viscosity of solution. The gel point is 50-90^{0}C depending upon the grade of material. HPMC powder should be stored in a well-closed container, in a cool, dry place.

Incompatabilites:

It is incompatible with some oxidizing agents. Since it is non-ionic, hydrolxypropyl methylcellulose will not complex with metallic salt and ionic organics to form insoluble precipitates.

Applications:

Widely used in oral and topical pharmaceutical formulations. In oral products, it is primarily used as a tablet binder, in film coating and as an extended release tablet matrix. Concentrations of between 2-5% w/w may be used as a binder in either wet or dry granulation processes. It is also used a suspending agent and thickening agent in topical formulations, particularly ophthalmic preparations. Used as adhesive in plastic bandages and as wetting agent for hard contact lenses.

4.4. SODIUM STARCH GLYCOLLATE: [23]

Nonproprietary Names

BP **:** Sodium starch glycolate.

USPNF **:** Sodium starch glycolate.

Synonyms :

Carboxy methyl starch, sodium salt, explo tab, primojel.

Description: Sodium salt of carboxymethyl ether of starch. White to off-white, tasteless, odorless, relatively free flowing powder. Practically insoluble in organic solvents. Absorbs water rapidly, resulting in swelling which leads to rapid disintegration of tablets and granules.

Molecular Formula **:** $C(CH_2CO_2Na)_3$ (CH_2COO_2Na)

Functional Category **:** Disintegrant, Suspending agent, Gelling agent

Density (bulk) **:** 0.85g/cm^2.

Density (tapped) **:** 1.000g/cm^2.

Chemical Name **:** Sodium carboxy methyl starch

Empirical Formula :

The BP 1993 states that sodium starch glycolate is the sodium salt of a poly-α-glucopyranose in which some of the hydroxyl groups are in the form of the carboxymethyl ether. The USPNF XVII states that it is the sodium salt of a carboxy methyl ether of starch.

Molecular Weight:

The molecular weight is typically 500000 -1000000. Sodium starch glycolate may be characterized by the degree of substitution and cross linking.

Applications:

Dissolution aid for Tablets, capsules and pellets recommended concentration 1.0 – 4.0%. May need to use up to 6.0% in wet granulation formulations, normally effective intra granularly. However, may be more effective if added 50% intra granularly, and 50% extra-granularly (in the final dry mixture).

5. AIM AND PLAN OF WORK

Carvedilol is Beta-adreno receptor antagonist which is used in treatment of hypertension and mainly in the treatment of congestive heart failure.

It is given as oral dosage form in the treatment of congestive heart failure and the management of hypertension. Its short biological half life 6 hrs and frequent administration (usually two times a day) make it a potential candidate for sustained release preparations.

The bioavailability of Carvedilol is 25 %.

Because of such pharmacokinetic characteristic the conventional dosage forms of the drug suffer the drawbacks of typical immediate release tablets. To overcome these drawbacks and also to overcome the side effects of the drug sustained release tablets can be prepared.

5.1. THE SCOPE OF THE PRESENT WORK:

- To provide a drug delivery system, which provides an initial burst release of the Carvedilol enough to take the plasma levels above the MEC and then provide a slow sustained release of the Carvedilol that maintains the plasma drug concentration above the MEC for an extended period of 12 hours.
- To provide a drug delivery system for continuous release of drug at controlled rate to maintain the therapeutic blood plasma concentration for a required period of time.

Finally to provide the drug delivery system which increases the patient compliance, effectiveness of therapy and reduces the chances of adverse effect and hypersensitivity of reaction by maintaining the plasma drug concentration at the same level with in therapeutic range for the required period of time.

5.2. PLAN OF WORK:

The present work was carried out to design and evaluate sustained-release bilayer tablets of Carvedilol, an antihypertensive drug. The bilayered sustained release tablets were prepared by wet granulation method using Ethyl Cellulose, Eudragit RSPO, HPMC 4000, lactose, magnesium stearate, talc and sodium starch glycolate. Keeping in view the objectives described above the following plan of work was adopted: -

- Preparation of standard calibration curve of Carvedilol.
- Drug-excipients compatibility study by FTIR spectrophotometer.
- Development of sustained release bilayer tablets using Ethyl cellulose, Eudragit RSPO, HPMC 4000 in three different concentrations by wet granulation method.
- Evaluation of blend characteristics of prepared granules (Pre-compression parameters)
    1. Angle of repose.
    2. Determination of bulk density.
    3. Determination of tapped density.
    4. Compressibility index.
    5. Hausner's Ratio.
- To perform evaluation parameters like (post-compression parameters)
    6. Appearance.
    7. Thickness.
    8. Hardness.
    9. Weight variation test.
    10. Friability test.
    11. Drug content uniformity.
    12. *In vitro* dissolution studies.
    13. Drug release kinetics data analysis.
    14. Stability studies of the optimized formulation.

6. METHODOLOGY

6.1. MATERIALS USED:

Table No. 1.

SR NO	MATERIALS	MANUFACTURERS/ SUPPLIERS
1	Carvedilol	Shasun Pharmaceuticals Ltd., Pondicherry.
2	Ethyl Cellulose	S.D. Fine Chem. Ltd., Mumbai
3	Hydroxy Propyl Methyl Cellulose 4000	Ajantha Pharma, Mumbai
4	Eudragit RSPO (Poly (ethylacrylate, methylmethacrylate) trimethyl ammonio ethyl methacrylate chloride.)1:2:0.1.	Ajantha Pharma, Mumbai
5	Sodium Starch Glycolate(SSG)	Loba Chemi Pvt., Ltd., Mumbai
6	Talc	S.D. Fine Chem. Ltd., Mumbai
7	Magnesium Stearate	S.D. Fine Chem. Ltd., Mumbai.
8	Starch	Merck Specialities, Mumbai.
9	Lactose	S.D. Fine Chem. Ltd., Mumbai.
10	Erythrosine Red	A to Z Pharmaceuticals, Chennai

6.2. INSTRUMENTS USED

Table No: 2

SR. NO.	INSTRUMENT	MANUFACTURER/SUPPLIER
1.	Electronic Balance	Sartorius, Germany.
2.	Rotary tablet Compression Machine (10 stages)	Rimek Mini Press I.
3.	Hardness Tester	Monsanto.
4.	Friability Test Apparatus	Roche friabilator.
5.	Vernier Calliper	Inox- Somet,Japan.
6.	Dissolution Apparatus.	Electro Lab. (USP XX III) (DTD – 06P).
7	Double BeamUV Spectrophotometer	Systronic Corporation, Mumbai.
8	FTIR Spectrophotometer	Perkin Elmer Spectrum, Japan.
10	Digital pH Meter	Eutech Instruments, Japan.
11	Hot Air Oven	Kemi, Mumbai.
12	Melting Point Apparatus.	Kemi, Mumbai.
13	Bulk Density Apparatus.	Kemi, Mumbai.

6.3. PREFORMULATION STUDIES[24]

6.3.1. MELTING POINT:

The melting point of Carvedilol was determined separately by using melting point apparatus.

6.3.2. PREPARATION OF STANDARD CURVE:

Preparation of standard curve of Carvedilol:

The Carvedilol **e**xhibits peak absorbance at 285 nm in dimethyl sulfoxide (DMSO) using Systronic double beam U.V. spectrophotometer.

Procedure for standard curve:

Weigh accurately 100mg of Carvedilol and dissolve it in 10 ml of DMSO, then make up the volume upto 100ml with DMSO (primary stock solution). From the primary stock solution take 10ml of solution and make up to 100ml with DMSO, this is the secondary stock solution. Several dilutions were made from this secondary stock solution, to obtain a concentration range of 1-5 µg/ml. The absorbance was measured at 285 nm using DMSO as blank and plotted to get the calibration curve.

6.3.3. Fourier Transform Infrared Spectrophotometer (FTIR):[25]

This is another parameter involved in the preformulation studies. This study involves finding out the compatibility of the drug with that of the polymer used. The study of drug with the excipients was determined by I.R. Spectroscopy (FTIR) using Perkin Elmer spectrum RX1 FT-IR spectrometer model. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of drug and other ingredients in the formulations were compared with that of the original spectra.

The FTIR of pure Carvedilol was taken and is shown in FTIR spectrum. Also the FTIR of Carvedilol with the polymers like Eudragit RSPO, Ethyl Cellulose and HPMC 4000 was taken individually. Also the FTIR of Carvedilol with Sodium Starch Glycolate was taken individually.

6.4. FORMULATION OF SUSTAINED RELEASE BILAYER MATRIX TABLETS OF CARVEDILOL[26]

Calculation of Loading and Maintenance dose:

The formulation involves the calculation of loading dose (Di), desired release rate(Ks), maintenance dose (Dm) and total dose required for Carvedilol bilayered SR matrix tablets as follows:

Oral dose : 25mg

Dosing Interval (τ) : 12 hrs

Elimination Half-life ($t_{1/2}$) : 6 hrs

Time of peak plasma concentration (t_p) : 1.5 hrs

Elimination rate constant (Ke) : $0.693/ t_{1/2}$

$= 0.693/6$

$= 0.1155$

Initial dose (Di): Css.Vd/F

But, Css $= F.Xo/Ke.Vd.\tau$

Thus, Di $= F.Xo/Ke.Vd.\tau * Vd/F$

$= Xo/ Ke.\tau$

$= 25/0.1155*12$

$= 18.03$

Desired rate of drug release (Ks): Di*Ke

$= 18.03*0.1155$

$=2.0824$ mg/hr

Maintenance dose (Dm): Ks* τ

$= 2.0824*12$

$= 24.988$ mg (25mg)

Corrected Initial dose (Di*): Di – ($Ks*t_p$)

= 18.03 – (2.0824*1.5)

= 14.90 mg (15mg)

Total dose (Dt): Dm+Di*

= 24.988+14.90

= 39.888 mg (40 mg)

6.4.1. PREPARATION OF SUSTAINED RELEASE BILAYER MATRIX TABLETS OF CARVEDILOL:[13,27,28]

The bilayer tablets of Carvedilol were prepared by the wet granulation method. The drug and polymers for both fast release and sustaining layer were passed through sieve number 44 before their use in the formulation.

Preparation of Immediate Releasing (Loading Dose) Layer:

Wet granulation method was followed to formulate the immediate release granules containing Carvedilol. Fast releasing granules was prepared by mixing Carvedilol with Sodium Starch Glycolate as disintegrating agent and starch paste as binder (which was previously mixed with Erythrosine Red as a colouring agent). The cohesive mass was passed through sieve number 22, and then it was dried at 60°C for half an hour in an oven. The granules were mixed with excipients like talc and magnesium stearate.

Preparation of sustained release layer.

The same wet granulation method was followed to formulate the sustained release granules containing Carvedilol. The drug was mixed with different polymers namely Eudragit RSPO, Ethyl Cellulose and HPMC 4000. Three different ratios of drug with polymer was selected (1:1, 1:2, 1:3) for each of the polymer, and totally nine formulations was formulated and named as from F1 – F3, F4–F6, F7–F9 containing HPMC 4000, Ethyl Cellulose, Eudragit RSPO respectively. Lactose was mixed with each drug polymer ratio. Starch paste (10%w/v) was added as binder. Excipients like talc and magnesium stearate was added to each of the formulations.

Compression of bilayer tablet

Required quantity of granules containing Carvedilol for the sustained release layer was first compressed lightly using a rotary tablet punching machine equipped with 11/32 round punch. Over this compressed layer, the required quantity of granules containing Carvedilol as fast release layer was placed and was compressed to obtain bilayer matrix tablets of Carvedilol.

Parameters fixed for tablet:

1. Tablet weight : 300 mg ± 20mg
2. Thickness : 2.4 ± 0.5 mm
3. Hardness : 4.2 ± 0.5 kg/cm^2
4. Friability : Not more than 1%.

Formulas of bilayered matrix tablets of carvedilol:

Formula of immediate releasing layer.

Table No. 3

INGREDIENTS	QUANTITY FOR A SINGLE TABLET(mg)
Carvedilol	15
Sodium Starch Glycolate	5
Starch Paste (10%)	10
Lactose	65
Magnesium Stearate	2
Talc Powder	3
Erythrosine Red	q.s

FORMULA OF SUSTAINED LAYER:

Table No. 4

Form Code	Carvedilol	HPMC 4000	Ethyl Cellulose	Eudragit RSPO	Lactose	Starch Paste	Talc	Magnesium Strearate
F1	25	12.5	-	-	157.5	q.s.	3	2
F2	25	25	-	-	145	q.s.	3	2
F3	25	37.5	-	-	132.5	q.s.	3	2
F4	25	-	12.5	-	157.5	q.s.	3	2
F5	25	-	25	-	145	q.s.	3	2
F6	25	-	37.5		132.5	q.s.	3	2
F7	25	-	-	12.5	157.5	q.s.	3	2
F8	25	-	-	25	145	q.s.	3	2
F9	25	-	-	37.5	132.5	q.s.	3	2

All weights are taken in mg

6.5. EVALUATION OF BLEND CHARACTERISTICS OF CARVEDILOL GRANULES: [29,30]

1. Angle of repose:

The flow property of the granules was determined by measuring the Angle of Repose. It is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane. Values of θ are rarely less than 20^o, and values of up to 40^o indicate reasonable flow potential. Above 50^o, however, the powder flows only with difficulty if at all.

$$\theta = \mathbf{Tan^{-1}\ (h/r)}$$

Where,

h = Height the pile.

r = Radius of the pile.

θ = Angle of repose.

A funnel was fixed in a holder; the tip of the funnel was placed at a height of 6 cms from the surface. A graph sheet was placed below the funnel. 5 gms of the sample was taken and was passed slowly through the funnel. The height of the powder heap formed was measured. The circumference of the heap formed was drawn with a pencil on the graph paper. The radius was determined and the angle of response was determined using the given formula. The same procedure was repeated 3 times for each sample.

2. Determination of bulk density and tapped density:

20 g of the powder (W) from each formula was introduced individually into a 100ml of measuring cylinder. After that the initial volume was noted, the cylinder was kept in bulk density apparatus for tapping. The tapping was continued for 100 times and the change in volume was noted.

The bulk density, and tapped density were calculated using the following formulas: -

Bulk density = W / V_0

Tapped density = W / V_f

Where,

W = Weight of the powder.

V_0 = Initial volume.

V_f = Final volume.

The results were presented in the table no:10

3. Compressibility index (Carr's index):

Compressibility index is an important measure which can be obtained from bulk and tapped densities. Theoretically, the less compressible a material the more flowable it is.

This shows that a material having value of less than 18 % is defined as the free flowing material.

$$C_I = 100 (V_0 - V_f) / V_0$$

Where,

C_I = Compressibility index.

4. Hausner's Ratio:

This indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

$$\text{Hauser's Ratio} = (W / V_f) / (W / V_0)$$

Where,

W / V_f = Tapped density.

W / V_0 = Bulk density.

Thus,

Hauser's Ratio = Tapped density/Bulk density.

6.5.1. EVALUATION OF BILAYERED TABLETS OF CARVEDILOL: [12, 13,28]

The following evaluations tests were performed for the prepared tablets of bilayered tablets containg Carvedilol:

Thickness, Hardness, Friability and Weight variation test.

Content uniformity test.

In-Vitro drug release study.

1. Tablet Thickness:

The thickness of the tablet was measured with Vernier Calliper. Five tablets were selected from each formulations and the test was performed.

2. Hardness Test:

Hardness test was carried out by using "Monsanto" hardness tester. Five tablets were randomly selected from each of the formulations and the test was carried out.

3. Friability Test:

"Roche" friabilator is used to determine the friability of the tablets. For determining the friability of the tablets 10 tablets were taken and weighed. After weighing the tablets were placed in the Roche friabilator and was allowed for the combined effects of abrasion and shock by utilizing a plastic chamber which was then allowed to revolve at 25 rpm for 4 minutes, this drops the tablets from a height of six inches with each revolution. After undergoing this procedure the tablets were dedusted and reweighed.

Friability can be determined by

$$F = 100\ (1-W_t/W_o)$$

Where,

W_o = weight of tablets before friability test.

W_t = weight of tablets after friability test.

4. Weight Variation Test:

Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual tablet's weights should deviate from the average weight by more than the percentage deviation shown in table and none should deviates by more than twice the percentage.

WEIGHT VARIATION TOLERANCES FOR UNCOATED TABLETS.

Table No. 5

S. No.	Average weight of Tablets (mg)	Maximum percentage difference allowed
1.	130 or Less	10
2.	130 to 324	7.5
3.	More than 324	5.0

% Maximum positive deviation = $(W_H - A/ A) \times 100$

% Minimum negative deviation = $(A-W_L/ A) \times 100$

Where,

W_H = Highest weight in mg.

W_L = Lowest weight in mg.

A = Average weight of tablet in mg.

5. Drug content uniformity: [27,31,32]

Ten tablets were finely powdered and an amount equivalent to 50 mg of Carvedilol was weighed accurately and transferred to a 100 ml volumetric flask, then 70 ml of ethanol was added. The flask was shaken for 10 min. Finally, the volume was made up to the mark with ethanol. The mixture was then filtered and 1 ml of the filtrate was diluted with ethanol to obtain a solution containing about 10 – 50 µg/ml of

Carvedilol and analyzed at 285 nm using a double beam UV/Visible spectrophotometer and ethanol as blank.

6. *In vitro* dissolution studies

In vitro dissolution test for the tablet of each formulation was carried out using USP dissolution type II apparatus using paddle, fixing the tablet to the paddle at 50 rpm. The dissolution was carried out using 900 ml of Acid buffer (pH 1.2) for the first 2 hrs which was then followed by Phosphate buffer (pH 6.8) for the remaining hours. The temperature was maintained at 37 ± 0.2 °C. 5ml of the sample was withdrawn at different time intervals, *i.e*. 5, 15, 30, 60, 120, 180, 240, 300, 360, 480, 600 and 720 min, and the same quantity was replaced with freshly prepared acid buffer and phosphate buffer respectively. The withdrawn sample was filtered through Whatmann filter paper. Samples were suitably diluted and release of the drug was determined using UV/Visible spectrophotometer under the wavelength of 285nm.

Details of dissolution test:

Dissolution test apparatus	:	USP
Speed	:	50 rpm
Stirrer	:	Paddle type
Volume of medium	:	900 ml
Aliquot taken at each time interval	:	5 ml
Medium used	:	Acid buffer (pH 1.2),
	:	Phospahte buffer (pH 6.8).
Temperature	:	37 ± 0.5 ^{0}C

***In vitro* dissolution studies for marketed tablet:**

In order to compare the drug release rate of the bilayer tablet with the marketed tablet the dissolution study of the marketed tablet was carried out in the same condition as mentioned above but only in phosphate buffer (pH 6.8).

6.5.2. KINETIC ANALYSIS OF IN-VITRO RELEASE RATES OF BILAYER TABLETS OFCARVEDILOL: [33]

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows: -

1. Zero - order kinetic model: This follows, Cumulative % drug released Vs time.
2. First – order kinetic model: This follows, Log cumulative percent drug remaining Vs time.
3. Higuchi's model: This follows, Cumulative percent drug released Vs square root of time.
4. Korsmeyer equation / Peppa's model: This follows, Log cumulative percent drug released Vs log time.

1. Zero order kinetics:

Zero order release would be predicted by the following equation: -

$A_t = A_0 – K_0t$

Where,

A_t = Drug release at time 't'.

A_0 = Initial drug concentration.

K_0 = Zero - order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release Vs time, if the plot is linear then the data obeys Zero – order kinetics and its slope is equal to Zero order release constant K_0.

2. First Order Kinetics:

First – order release would be predicted by the following equation: -

$$\text{Log } C = \log C_0 - Kt / 2.303$$

Where,

C = Amount of drug remained at time't'.

C_0 = Initial amount of drug.

K = First – order rate constant (hr^{-1}).

When the data plotted as log percent drug remaining Vs time, yields a straight line, this indicates that the release follows first order kinetics. The constant 'K_1' can be obtained by multiplying 2.303 with the slope value.

3. Higuchi's model:

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation: -

$$Q = [D\varepsilon / \tau (2 A - \varepsilon Cs) Cst]^{½}$$

Where,

Q = Amount of drug released at time't'.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

ε = Porosity of the matrix.

τ = Tortuosity.

t = Time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'D', 'Cs' and 'A' are constant. Then equation becomes: -

$$Q = Kt^{1/2}$$

When the data is plotted according to equation i.e. cumulative drug release Vs square root of time yields a straight line, this indicates that the drug was released by diffusion mechanism. The slope is equal to 'K' (Higuchi's 1963).

4. Korsmeyer equation / Peppa's model:

To study the mechanism of drug release from the sustained-release matrix tablets of Diltiazem Hydrochloride, the release data was fitted to a well-known exponential equation (Korsmeyer equation/ peppa's law equation), which is often used to describe the drug release behaviour from polymeric systems.

$M_t / M_\alpha = Kt^n$

Where,

M_t / M_α = The fraction of drug released at time't'.

K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

And we get: -

$$\text{Log } M_t / M_\alpha = \text{Log } K + n \text{ Log } t$$

MECHANISM OF DRUG RELEASE AS PER KORSMEYER EQUATION / PEPPA'S MODEL.

Table No. 6

S. No.	n Value	Drug release
1.	< 0.45	Fickian release
2.	0.45 <1.0	Non – Fickian release
3.	> 1.0	Class II transport

When the data is plotted as log of % cumulative drug released Vs log time, it yields a straight line with a slope equal to 'n'. For Fickian release 'n' = 0.45 while for anomalous (non - Fickian) transport 'n' ranges between 0.45 and 1.0.

6.6. STABILITY STUDIES OF THE OPTIMIZED FORMULATION

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life."

Hence the purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

ICH specifies the length of study and storage conditions:

Long term testing: $25^0C \pm 2^0C$ /60% RH ± 5% RH for 12 months.

Accelerated testing: $40^0C \pm 2^0C$ /75% RH ± 5% RH for 6 months.

Procedure:

In the present study, stability studies were carried out at $40^0C \pm 2^0C$ for a time period of 90 days for selected optimized formulations.

For stability study, the tablets were placed in an ambered coloured vials and sealed with aluminum foil. These sample containers were placed in desiccator.

Evaluation of samples:

The samples were analyzed for the following parameter,

Physical evaluation:

Appearance: The samples were checked for any change in colour at every week.

Hardness: The samples were tested for hardness at every week.

Chemical evaluation:

Drug content: The samples were checked for drug content.

Drug release: The samples were subjected to drug release studies.

7. RESULTS

7.1. PREFORMULATION STUDIES

7.1.1. Melting point:

The melting point of Carvedilol was found to be 114.2^{o}C, which is within the reported value (114 to 115^{o}C).

The melting point of both the drugs complies with their individual standards thus indicating the purity of the drug sample.

Photo 1. Shows the external appearance of the bilayer tablets of formulation F3 containing HPMC 4000.

7.1.2. Preparation of calibration curve of Carvedilol:

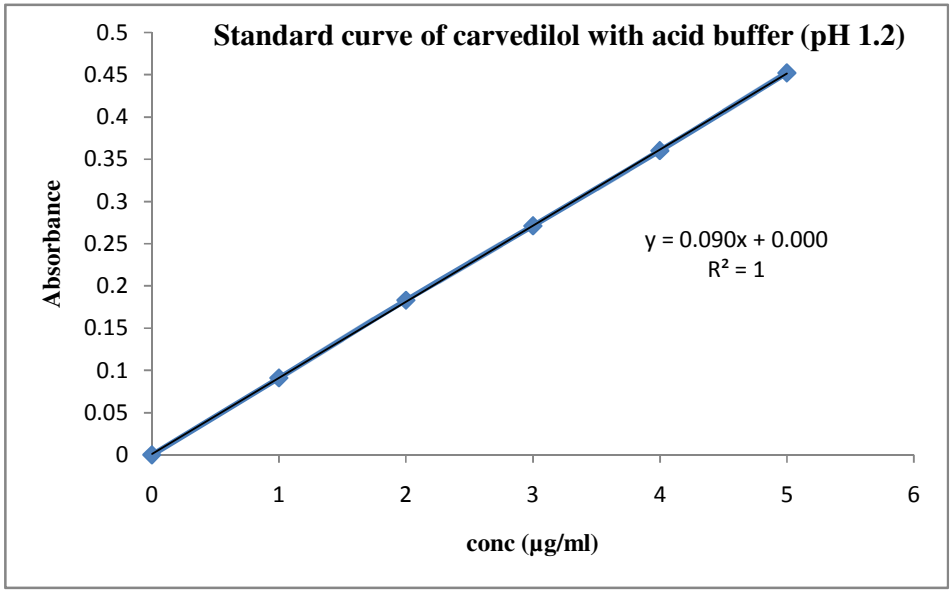
STANDARD CURVE OF CARVEDILOL IN ACID BUFFER (pH 1.2)

Table No: 7

Concentration (µg/ml)	Absorbance (nm)
1	0.091
2	0.183
3	0.271
4	0.360
5	0.452

STANDARD CURVE OF CARVEDILOL IN ACID BUFFER (pH 1.2)

Graph No: 1



Slope = 0.090

Correlation coefficient = 1.000

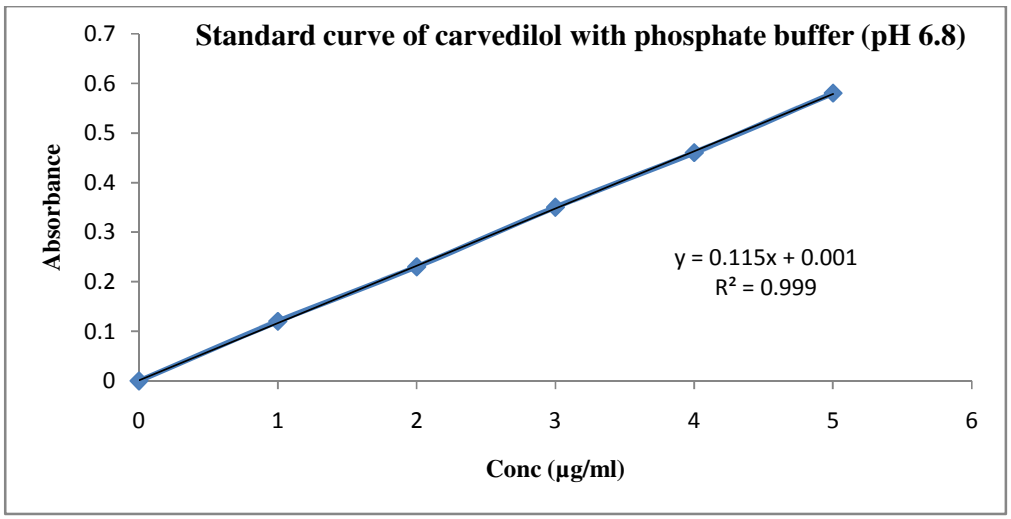
STANDARD CURVE OF CARVEDILOL IN PHOSPHATE BUFFER (pH 6.8)

Table No: 8

Concentration (µg/ml)	Absorbance (nm)
1	0.121
2	0.232
3	0.350
4	0.461
5	0.582

Standard curve of carvedilol in phosphate buffer (ph6.8)

Graph No: 2

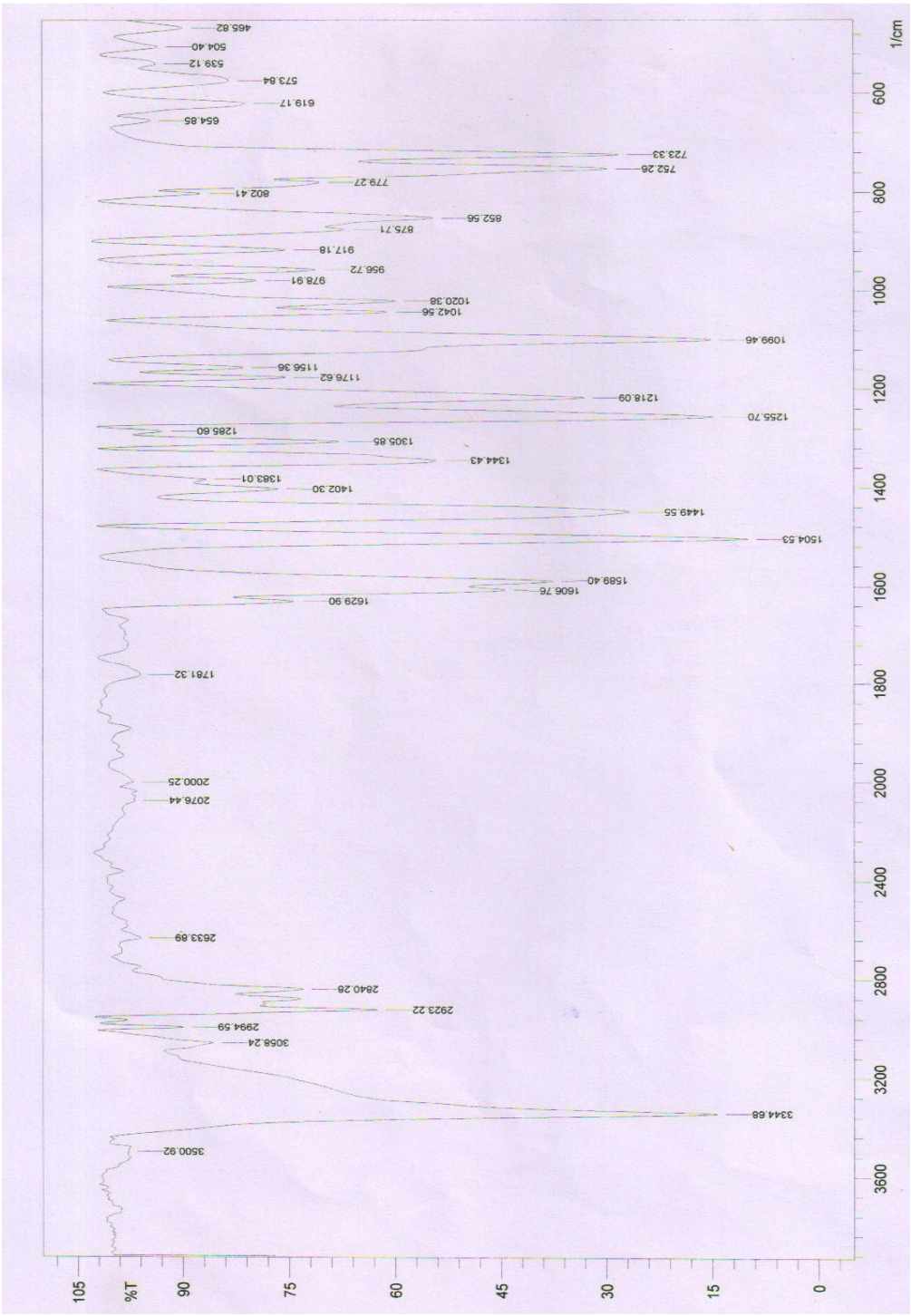


Slope = 0.1150

Correlation coefficient = 0.999

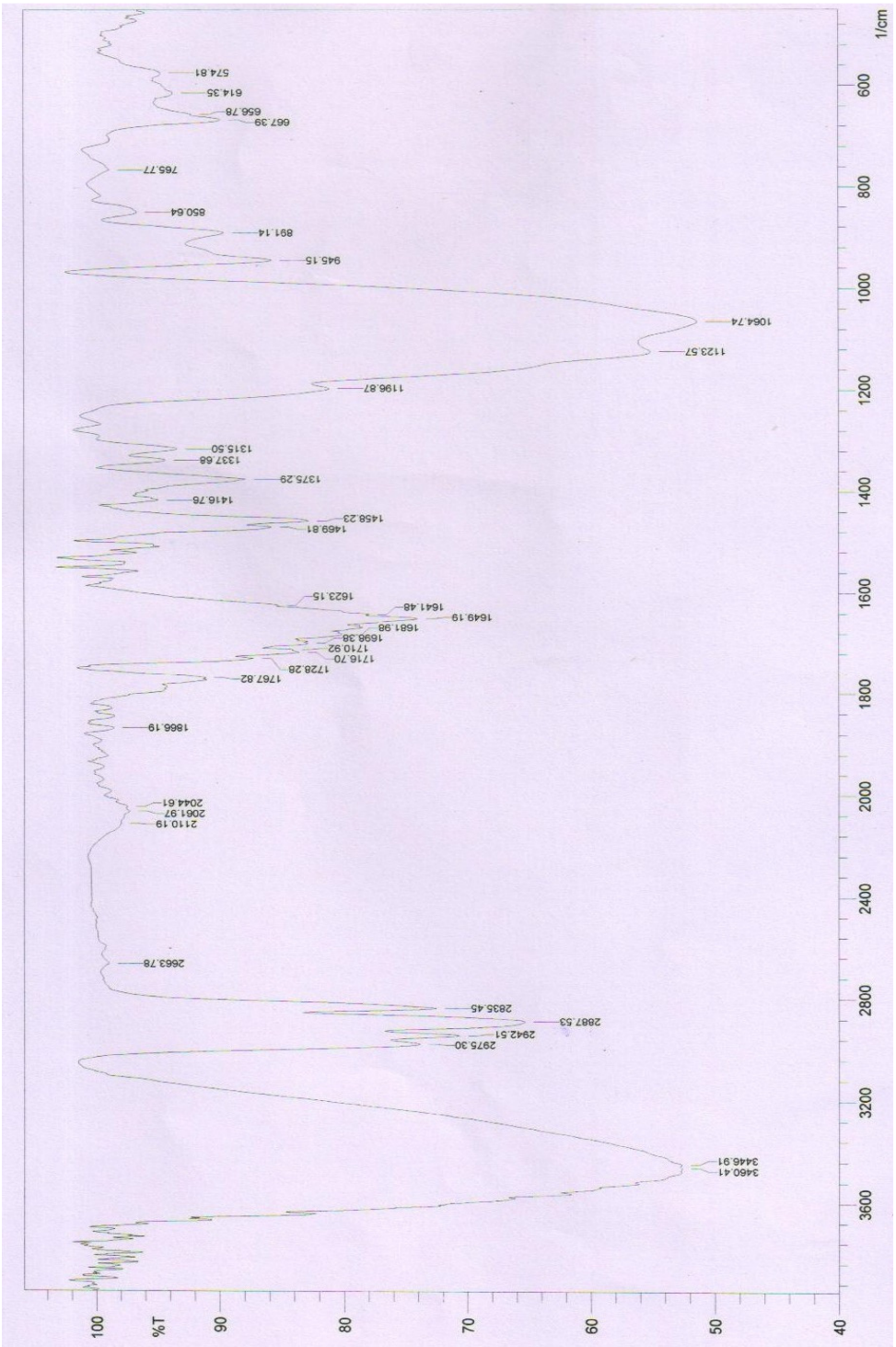
FTIR SPECTRA OF CARVEDILOL

Spectra no 7.1



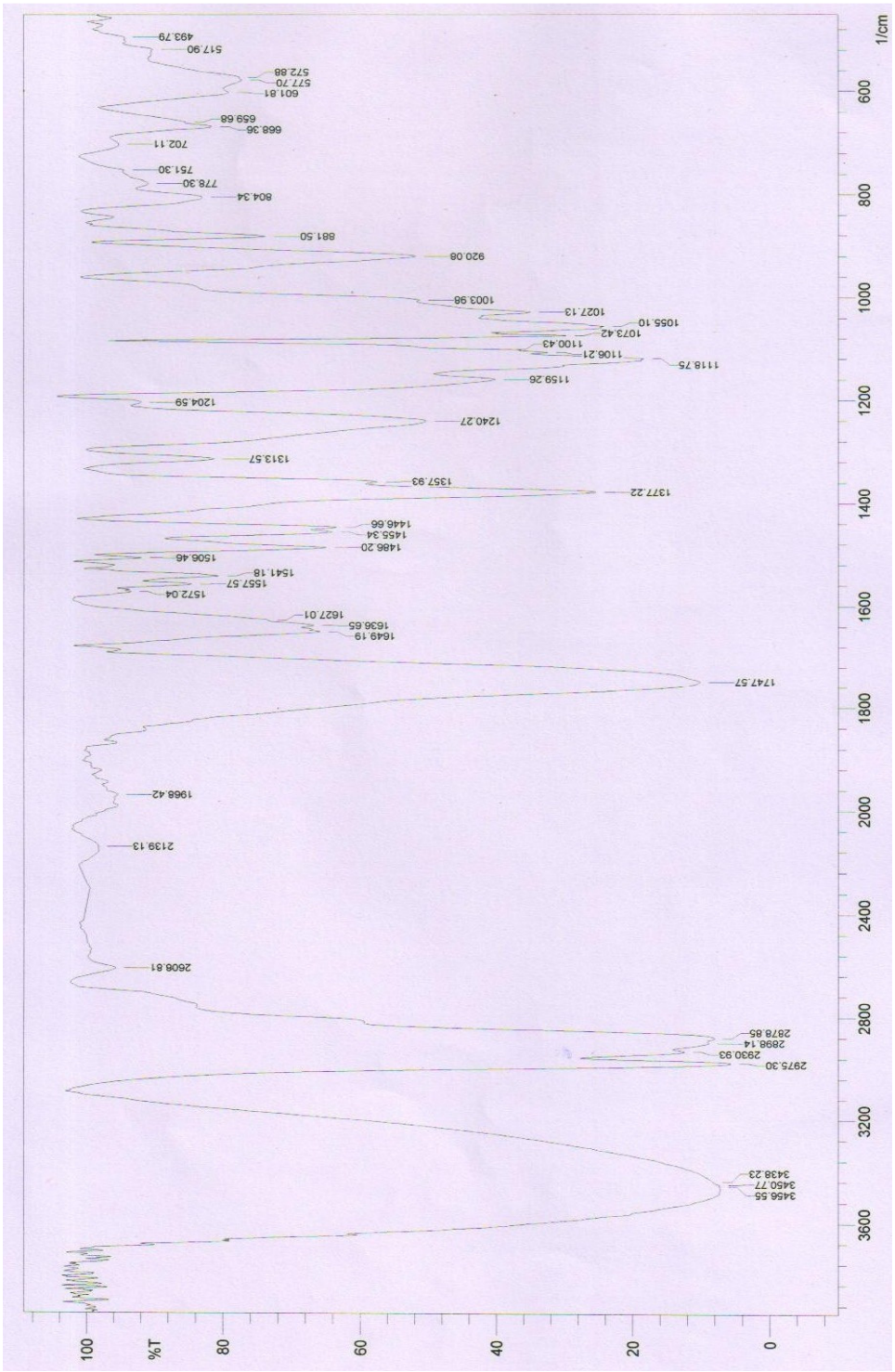
FTIR SPECTRA OF HPMC 4000

Spectra no 7.2



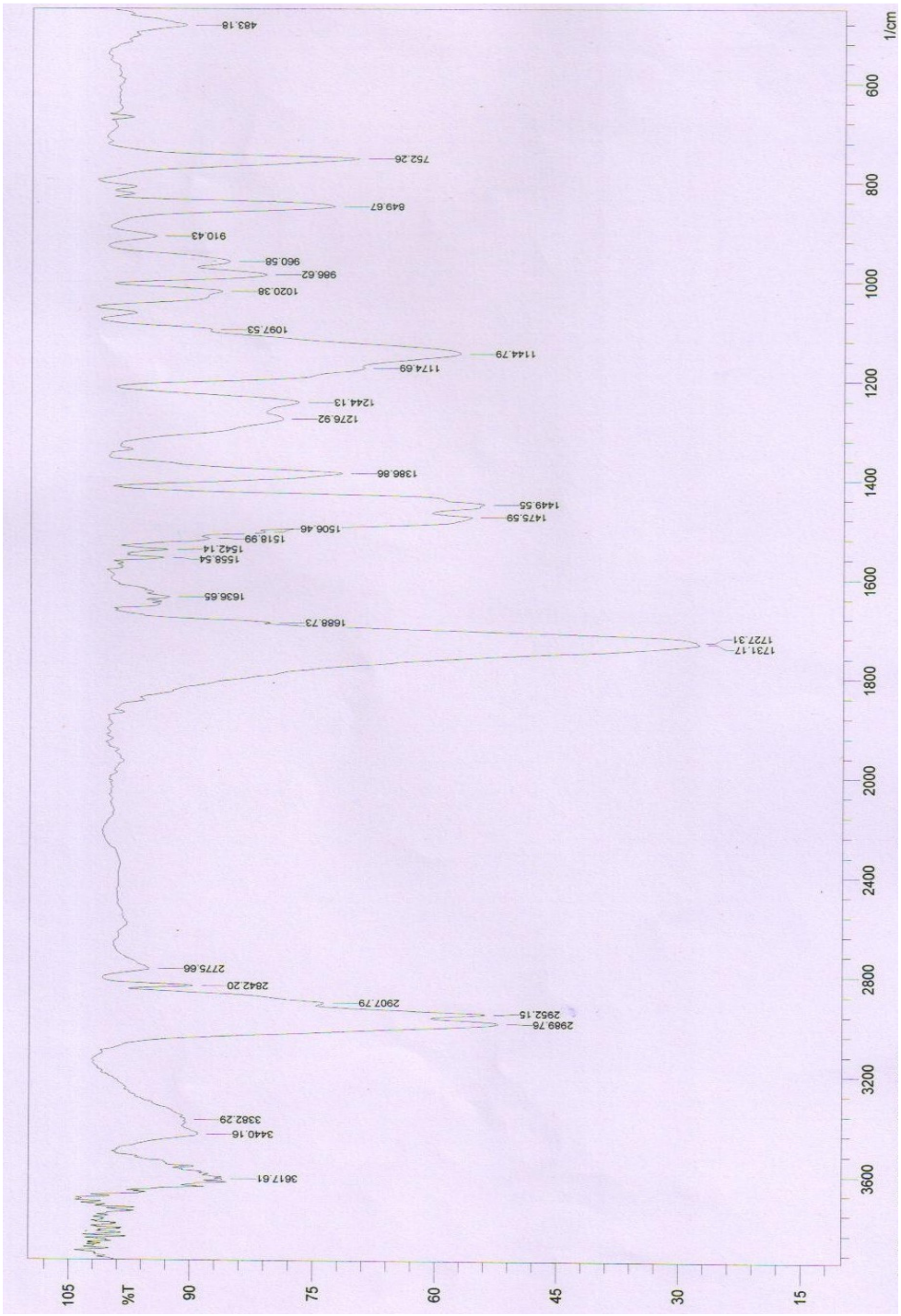
FTIR SPECTRA OF ETHYL CELLULOSE

Spectra no 7.3



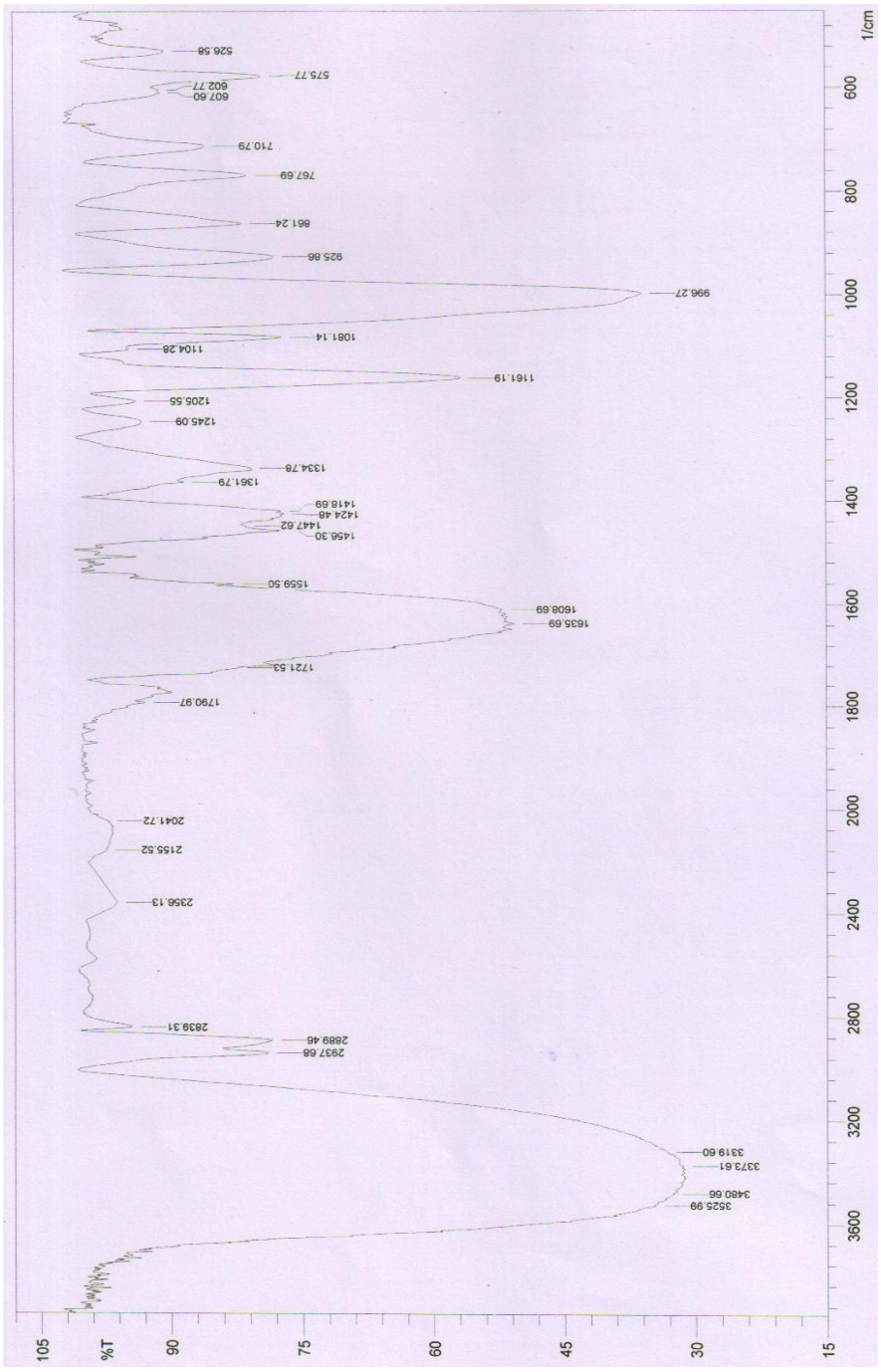
FTIR SPECTRA OF EUDRAGIT RSPO

Spectra no 7.4



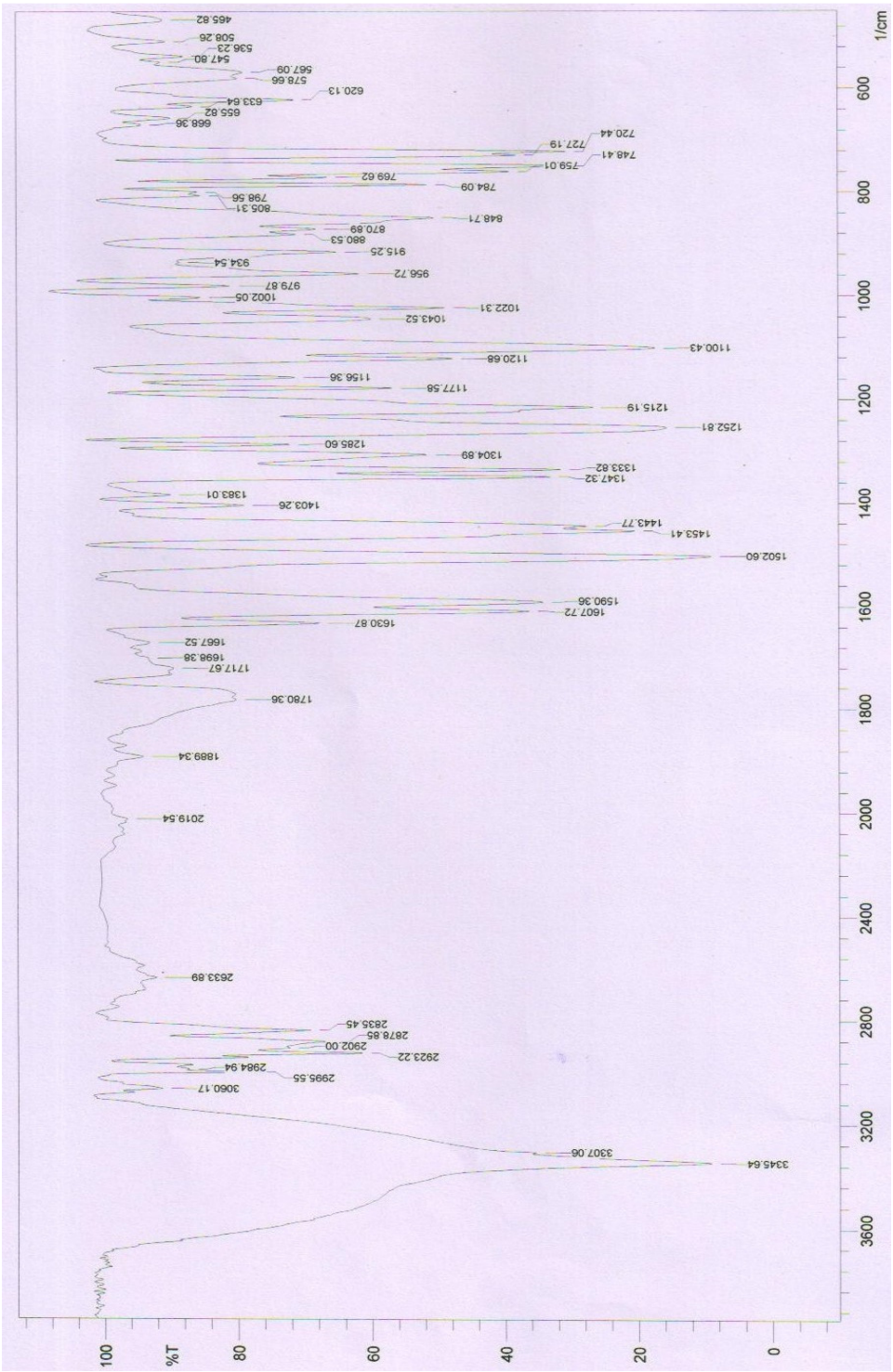
FTIR SPECTRA OF SODIUM STARCH GLYCOLATE

Spectra no 7.5



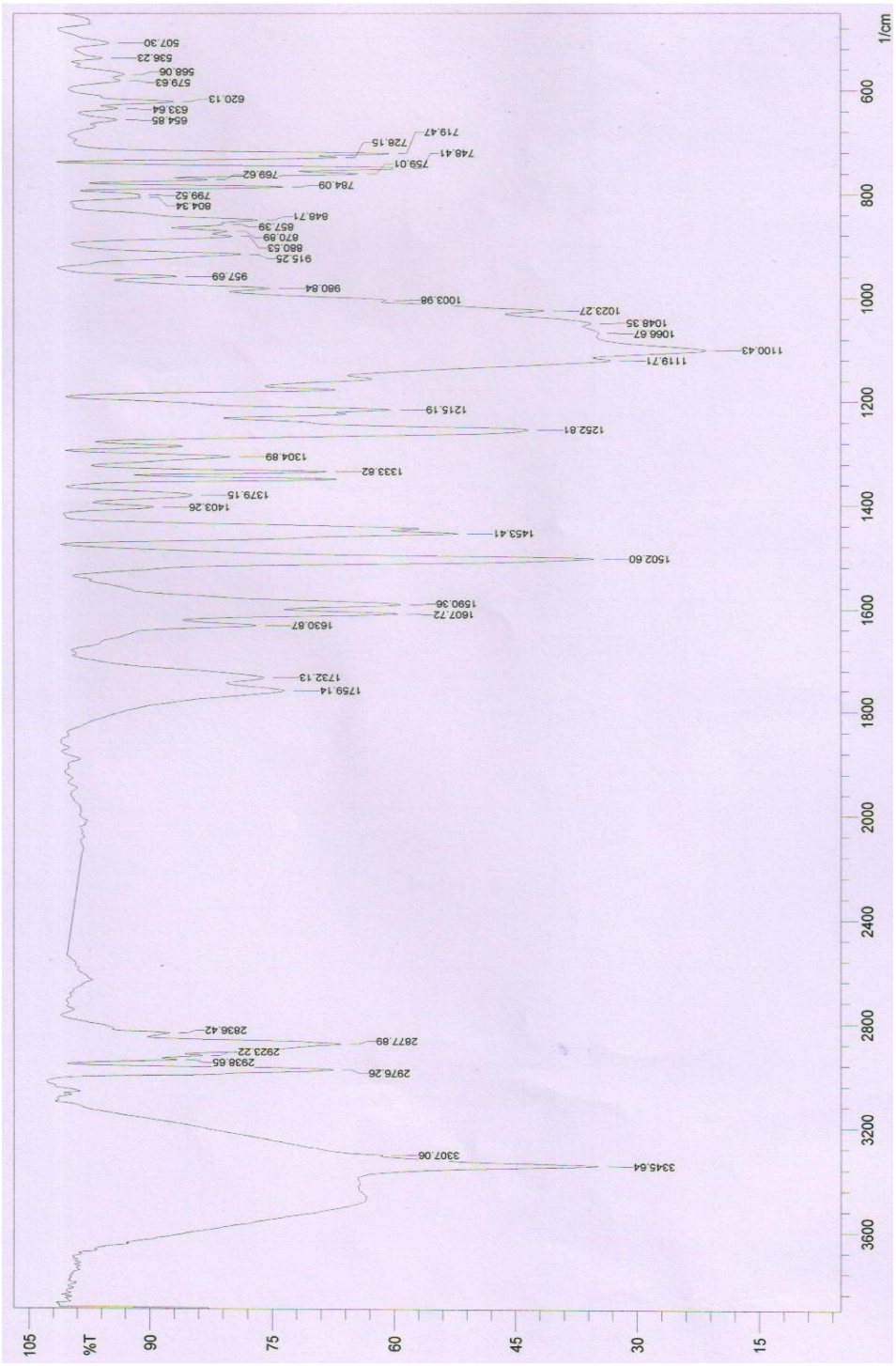
FTIR SPECTRA OF CARVEDILOL + HPMC 4000

Spectra no 7.6



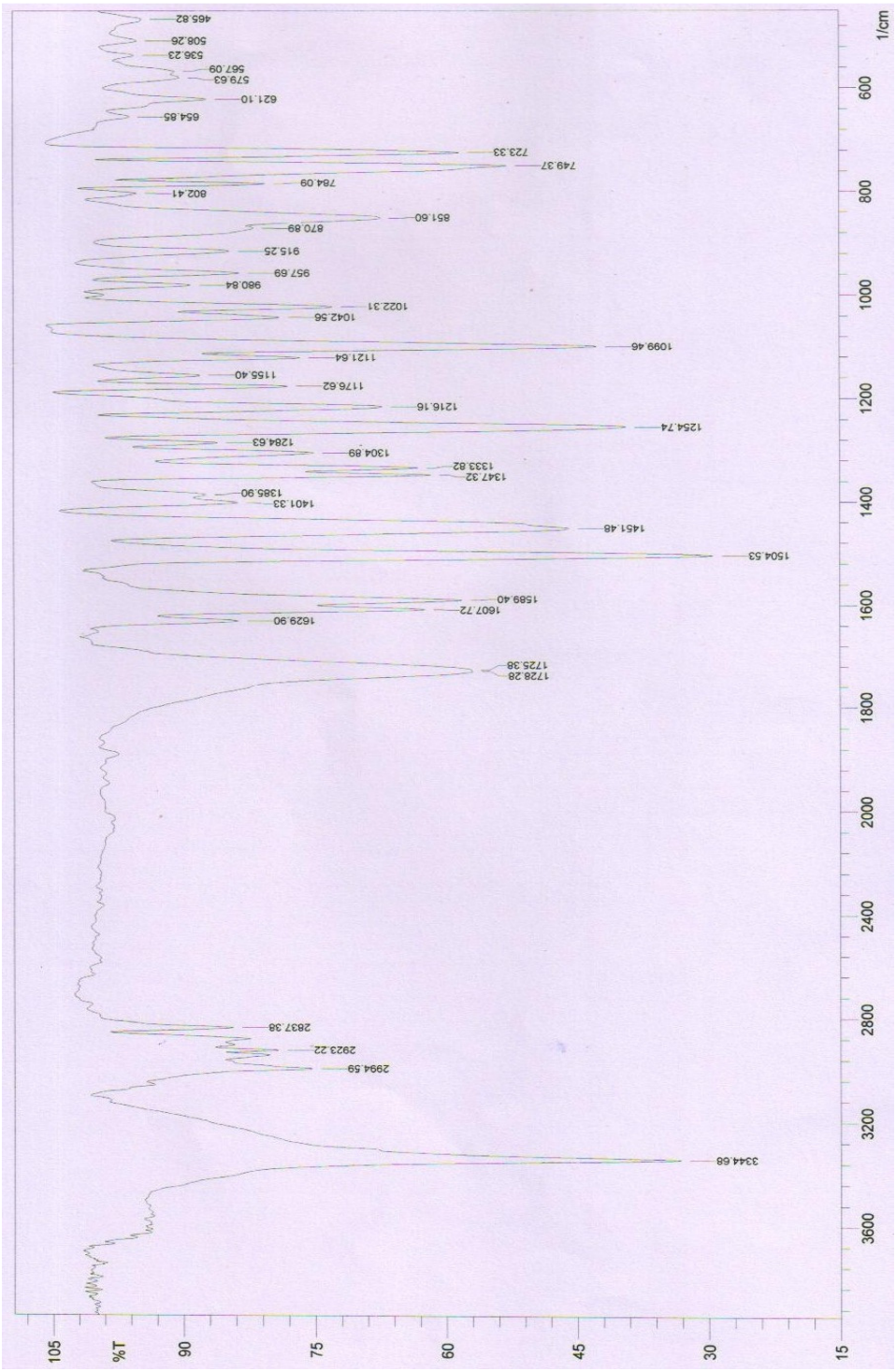
FTIR SPECTRA OF CARVEDILOL + ETHYL CELLULOSE

Spectra no 7.7



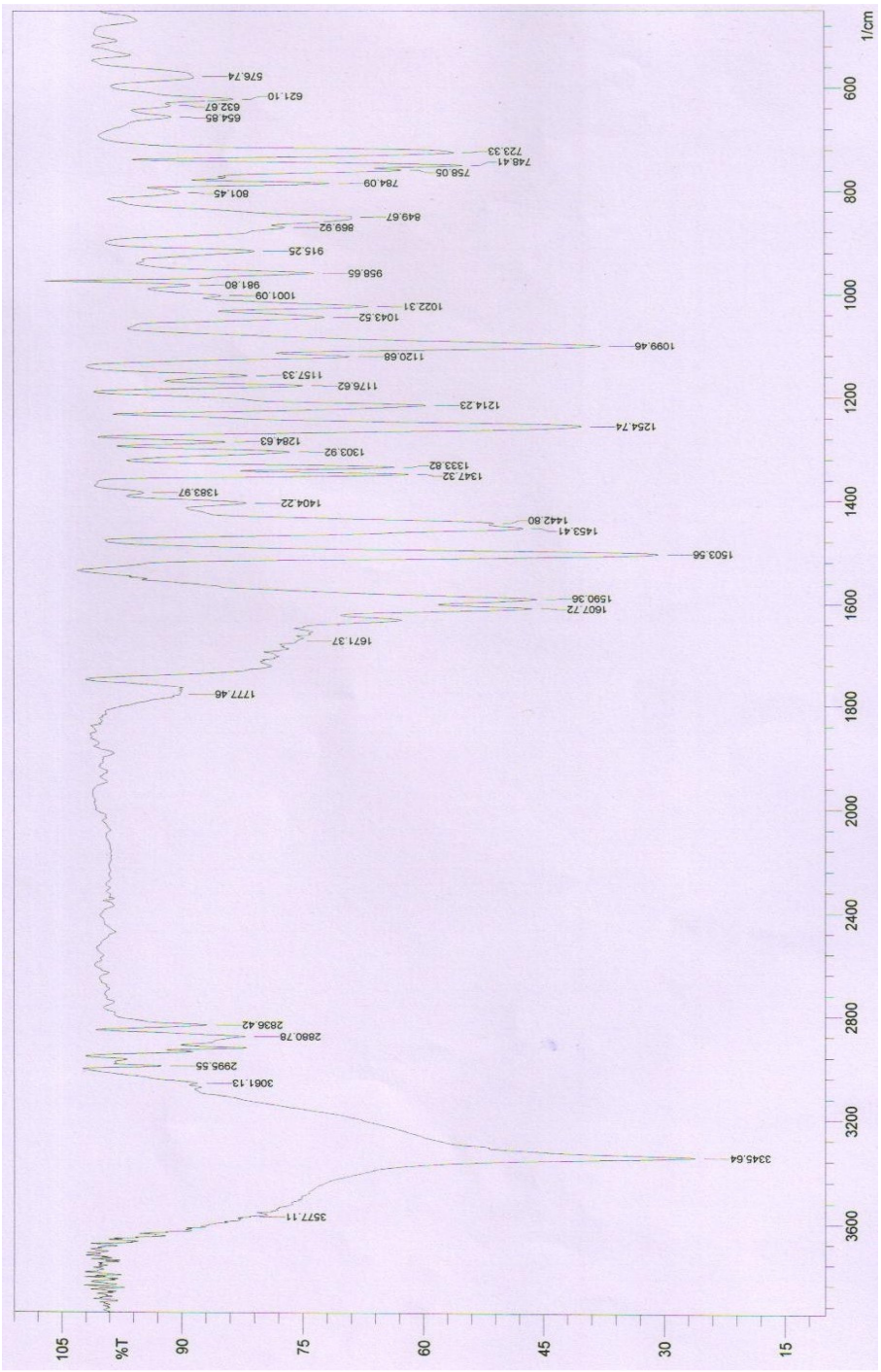
FTIR SPECTRA OF CARVEDILOL + EUDRAGIT RSPO

Spectra no 7.8



FTIR SPECTRA OF CARVEDILOL + SODIUM STARCH GLYCOLATE

Spectra no 7.9



ASSESMENT OF THE FUNCTIONAL GROUPS OF CARVEDILOL OBTAINED IN FTIR SPECTRA OF COMPATIBILITY STUDIES.

Table 9

S. NO	FUNCTIONAL GROUP	STANDARD IR RANGE cm^{-1}	ASSESMENT PEAKS OF PURE DRUG cm^{-1}
1	Secondary amine (N-H stretching)	3500-3300	3344.68
2	Secondary alcohol	1350-1260	1305.85
3	Aromatic	3050-3000	3058.24
4	C-H	2960-2850	2923.22
5	Aromatic hydrocarbons	1600	1606.76
6	Disubstituted (ortho)	770-735	752.26
7	-OCH3 stretching	Below 3000	2923.22
8	C=C stretching in aromatic nuclei	1700-1400	1449.55, 1504.53, 1589.40, 1606.76,1629.90

GRANULAR PROPERTIES OF FORMULATIONS

Table 10

Formulation Code	Angle of Repose	Bulk Density (gm/cm^2)	Tapped Density (gm/cm^2)	Compressibility Index (%)	Hauser's Ratio
F1	$23^0$14"	0.740	0.869	14.814	1.174
F2	$25^0$42"	0.714	0.800	10.714	1.120
F3	$24^0$33"	0.689	0.769	10.344	1.116
F4	$25^0$45"	0.769	0.869	11.538	1.130
F5	$26^0$38"	0.714	0.833	14.285	1.166
F6	$24^0$34"	0.689	0.800	13.793	1.161
F7	$23^0$44"	0.769	0.869	11.538	1.130
F8	$26^0$36"	0.740	0.833	11.111	1.125
F9	$24^0$44"	0.714	0.833	14.285	1.166

TABLETING PROPERTIES OF BILAYER TABLETS CONTAINING CAEVEDILOL

Table 11

Form Code	Evaluation Parameters					
	Thickness ±S.D. (mm)	**Hardness ±S.D. (Kg/cm^2)**	**Friability ±S.D. (%)**	**Average Weight variation**	**Disintegration (secs)**	**Drug Content (%)**
F1	2.43±0.05	4.3±0.15	0.197±0.010	300±2.08	33±2.64	91.66±1.52
F2	2.36±0.05	4.2±0.11	0.264±0.002	299±2.64	36±1.15	93.66±0.57
F3	2.40±0.10	4.2±0.05	0.652±0.006	301±3.00	37±1.15	97.33±1.15
F4	2.46±0.05	4.4±0.05	0.663±0.005	300±0.57	34±0.57	92.66±0.57
F5	2.46±0.05	4.3±0.05	0.265±0.001	298±3.46	37±1.00	95.00±1.00
F6	2.43±0.05	4.3±0.10	0.262±0.002	298±1.15	36±1.00	94.00±1.00
F7	2.33±0.05	4.3±0.10	0.317±0.023	301±0.57	37±0.57	93.66±1.52
F8	2.46±0.05	4.3±0.15	0.532±0.002	302±0.46	36±1.00	94.33±0.57
F9	2.43±0.05	4.4±0.10	0.525±0.005	298±2.00	36±0.57	96.33±0.57

DRUG RELEASE PROFILE FOR F1 FORMULATION CONTAINING HPMC 4000

Table 12

S. No	Formulation Type	Time (Mins)	Cumulative % Drug Release	% Drug Release
1	Immediate Release	5	1.19	11.90
2		15	5.21	20.10
3		30	8.85	34.20
4		60	12.06	13.20
5		120	16.78	62.30
6	Sustained Release	180	1.54	6.19
7		240	6.21	9.32
8		300	8.60	12.55
9		420	15.11	23.94
10		540	21.59	31.21
11		660	28.07	40.53

DRUG RELEASE PROFILE FOR F2 FORMULATION CONTAINING HPMC 4000

Table 13

S. No	Formulation Type	Time (Mins)	Cumulative % Drug Release	% Drug Release
1	Immediate Release	5	1.02	10.2
2		15	6.86	29.2
3		30	12.2	46.4
4		60	17.28	63.2
5		120	23.44	85.6
6	Sustained Release	180	0.79	3.19
7		240	4.02	6.44
8		300	9.62	16.02
9		420	18.97	29.92
10		540	31.93	48.89
11		660	50.66	76.88

DRUG RELEASE PROFILE FOR F3 FORMULATION CONTAINING HPMC 4000

Table 14

S. No	Formulation Type	Time (Mins)	Cumulative % Drug Release	% Drug Release
1	Immediate Release	5	1.08	10.8
2		15	5.12	20.2
3		30	9.98	39.8
4		60	16.02	60.2
5		120	24.00	89.90
6	Sustained Release	180	1.03	4.13
7		240	5.50	8.95
8		300	11.98	19.50
9		420	24.12	38.50
10		540	40.71	62.17
11		660	62.01	92.94

DRUG RELEASE PROFILE FOR F4 FORMULATION CONTAINING ETHYL CELLULOSE

Table 15

S. No	Formulation Type	Time (Mins)	Cumulative % Drug Release	% Drug Release
1	Immediate Release	5	1.12	11.20
2		15	5.10	19.90
3		30	9.35	36.80
4		60	16.14	62.30
5		120	23.29	85.30
6	Sustained Release	180	1.54	6.19
7		240	7.68	12.27
8		300	11.53	16.93
9		420	18.16	27.86
10		540	31.50	49.08
11		660	43.35	62.17

DRUG RELEASE PROFILE FOR F5 FORMULATION CONTAINING ETHYL CELLULOSE

Table 16

S. No	Formulation Type	Time (Mins)	Cumulative % Drug Release	% Drug Release
1	Immediate Release	5	1.08	10.80
2		15	6.96	29.40
3		30	12.26	46.60
4		60	17.34	63.40
5		120	23.70	86.80
6	Sustained Release	180	0.82	3.31
7		240	4.11	6.57
8		300	9.87	16.46
9		420	19.14	30.05
10		540	32.02	49.02
11		660	50.76	77.00

DRUG RELEASE PROFILE FOR F6 FORMULATION CONTAINING ETHYL CELLULOSE

Table 17

S. No	Formulation Type	Time (Mins)	Cumulative % Drug Release	% Drug Release
1	Immediate Release	5	1.00	10.00
2		15	4.80	19.00
3		30	9.70	39.00
4		60	15.74	59.20
5		120	23.16	86.20
6	Sustained Release	180	0.95	3.81
7		240	5.27	8.64
8		300	11.44	18.56
9		420	22.95	36.62
10		540	38.88	59.44
11		660	58.54	87.37

DRUG RELEASE PROFILE FOR F7 FORMULATION CONTAINING EUDRAGIT RSPO

Table 18

S. No	Formulation Type	Time (Mins)	Cumulative % Drug Release	% Drug Release
1	Immediate Release	5	1.13	11.30
2		15	5.15	20.10
3		30	9.39	36.90
4		60	16.21	62.60
5		120	23.38	85.60
6	Sustained Release	180	1.55	6.22
7		240	7.78	12.45
8		300	11.66	17.09
9		420	18.51	28.48
10		540	31.72	49.21
11		660	43.46	62.32

DRUG RELEASE PROFILE FOR F8 FORMULATION CONTAINING EUDRAGIT RSPO

Table 19

S. No	Formulation Type	Time (Mins)	Cumulative % Drug Release	% Drug Release
1	Immediate Release	5	1.07	10.70
2		15	6.93	29.30
3		30	12.21	46.40
4		60	17.28	63.20
5		120	23.60	86.40
6	Sustained Release	180	0.83	3.34
7		240	4.43	7.20
8		300	10.06	16.52
9		420	19.48	30.70
10		540	32.22	49.08
11		660	50.14	75.75

DRUG RELEASE PROFILE FOR F9 FORMULATION CONTAINING EUDRAGIT RSPO

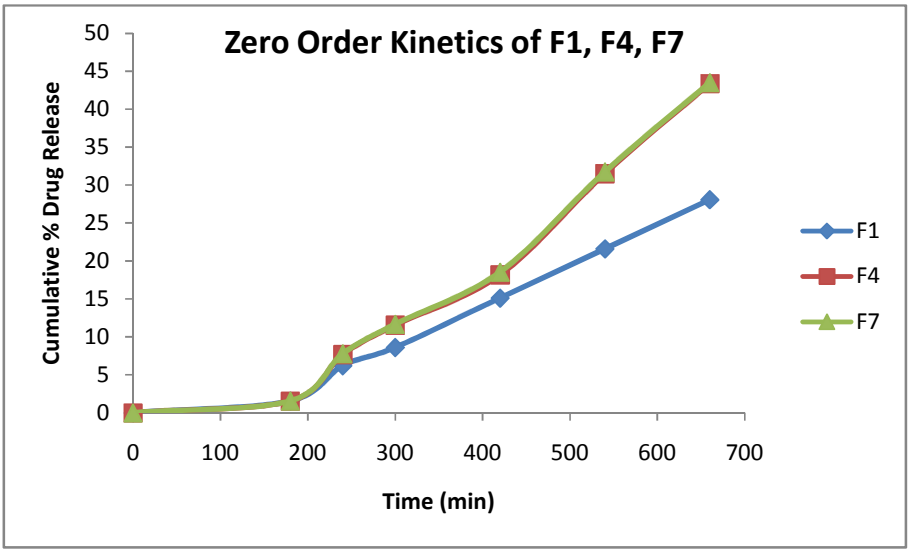
Table 20

S. No	Formulation Type	Time (Mins)	Cumulative % Drug Release	% Drug Release
1	Immediate Release	5	1.04	10.40
2		15	5.44	22.00
3		30	10.40	41.00
4		60	16.12	60.10
5		120	23.49	87.40
6	Sustained Release	180	0.96	3.85
7		240	5.31	8.70
8		300	11.50	18.65
9		420	23.46	37.59
10		540	39.49	60.19
11		660	60.20	90.31

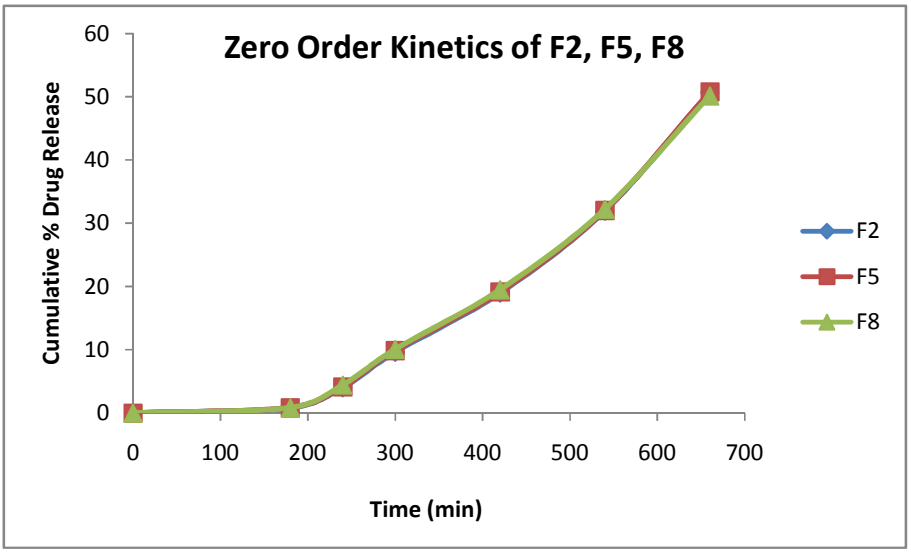
DRUG RELEASE PROFILE FOR MARKETED TABLET

Table 21

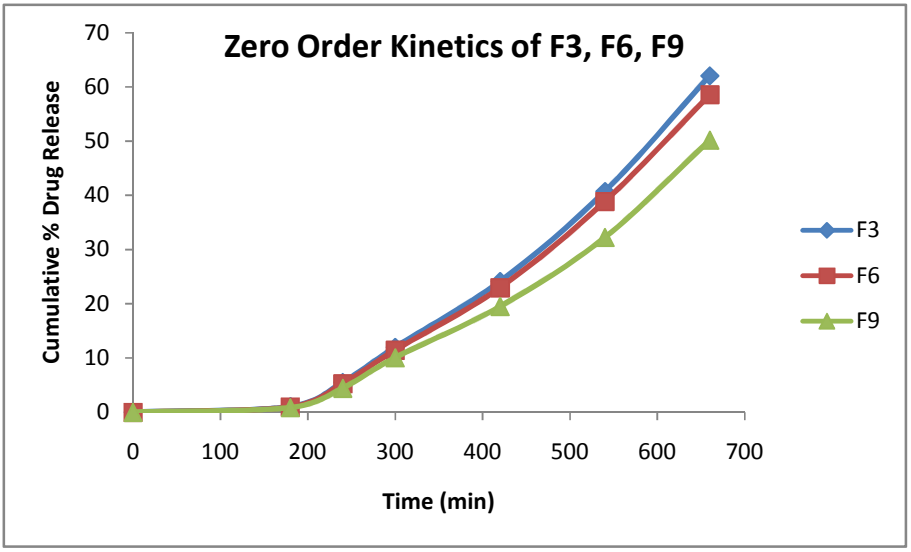
S. No	Formulation Type	Time (Mins)	Cumulative % Drug Release	% Drug Release
1	Conventional	30	1.95	7.82
2		60	7.46	11.01
3		180	16.27	27.04
4		300	29.45	45.39
5		420	45.46	68.24
6		720	65.03	95.94



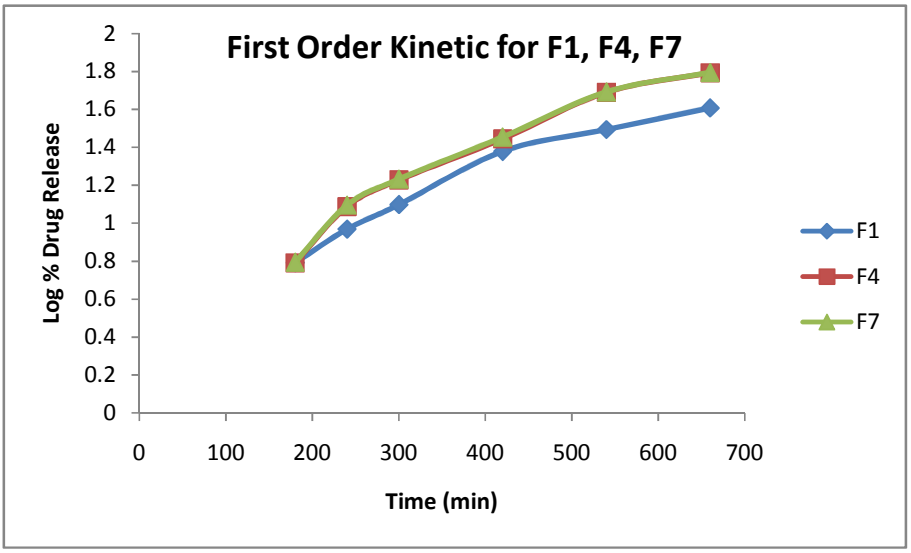
Graph 3: Shows zero order kinetics of F1, F4, F7



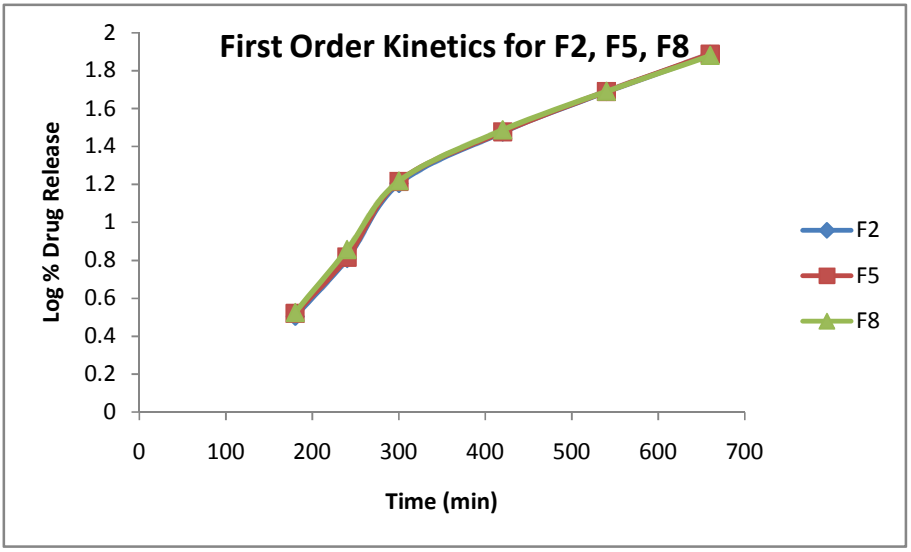
Graph 4: Shows zero order kinetics of F2, F5, F8



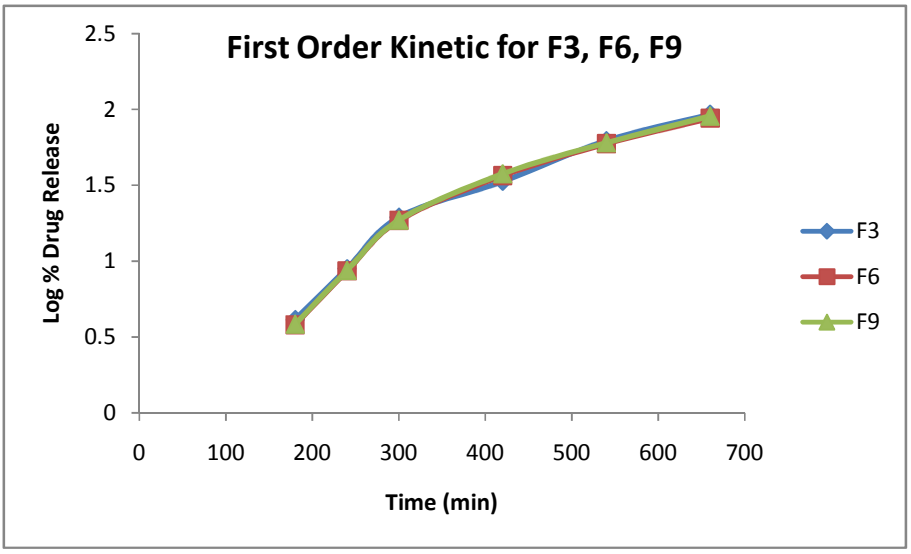
Graph 5: Shows zero order kinetics of F3, F6, F9



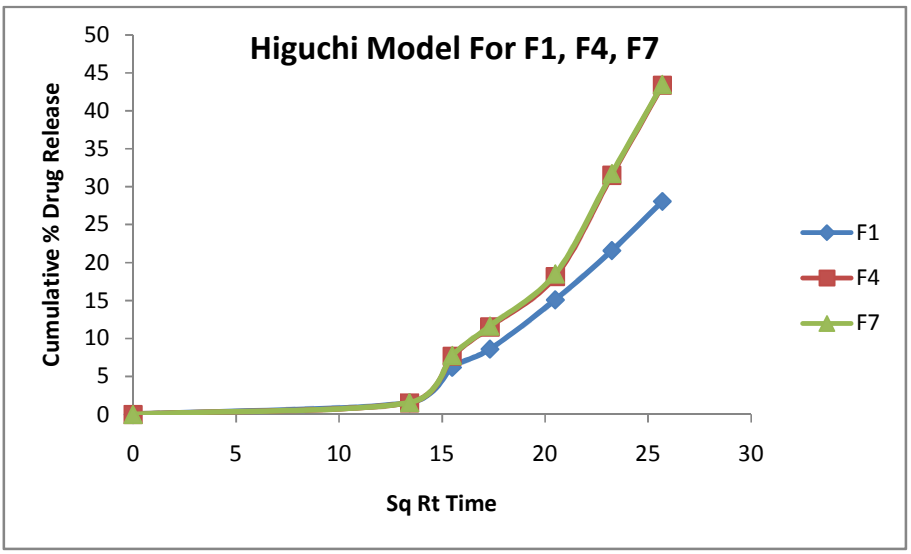
Graph 6: Shows first order kinetics of F1, F4, F7



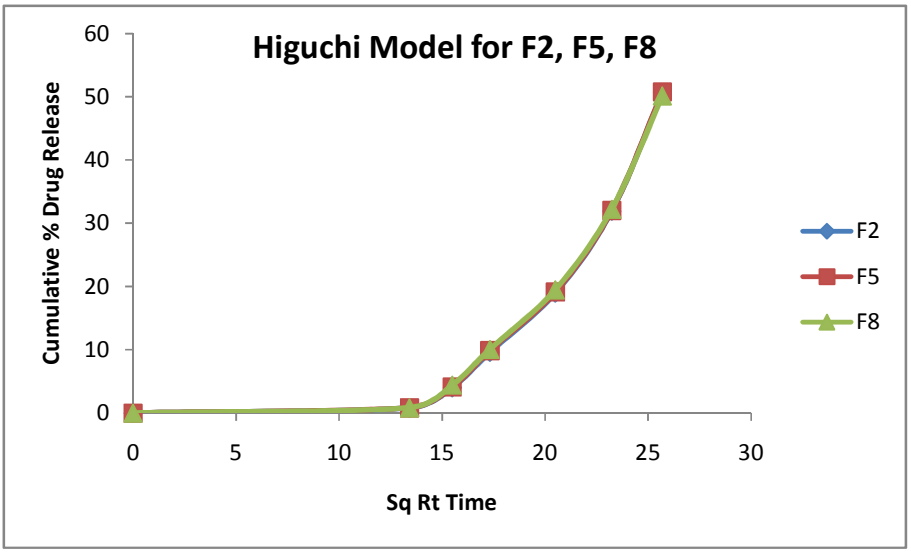
Graph 7: Shows first order kinetics of F2, F5, F8



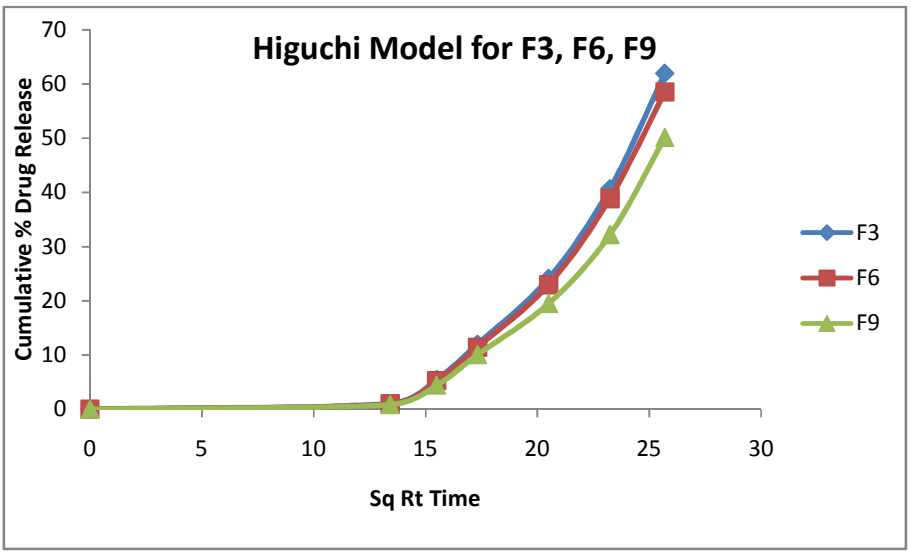
Graph 8: Shows first order kinetics of F3, F6, F9



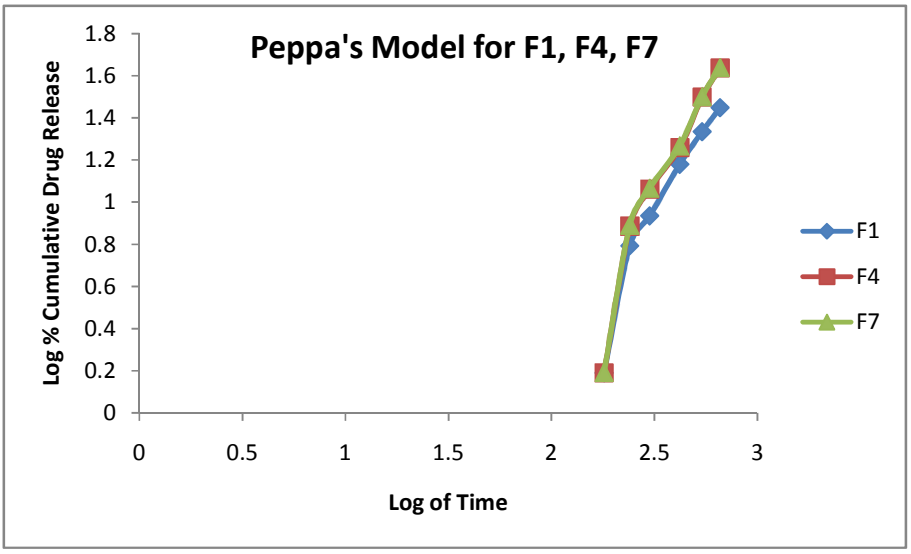
Graph 9: Shows higuchi model for F1, F4, F7



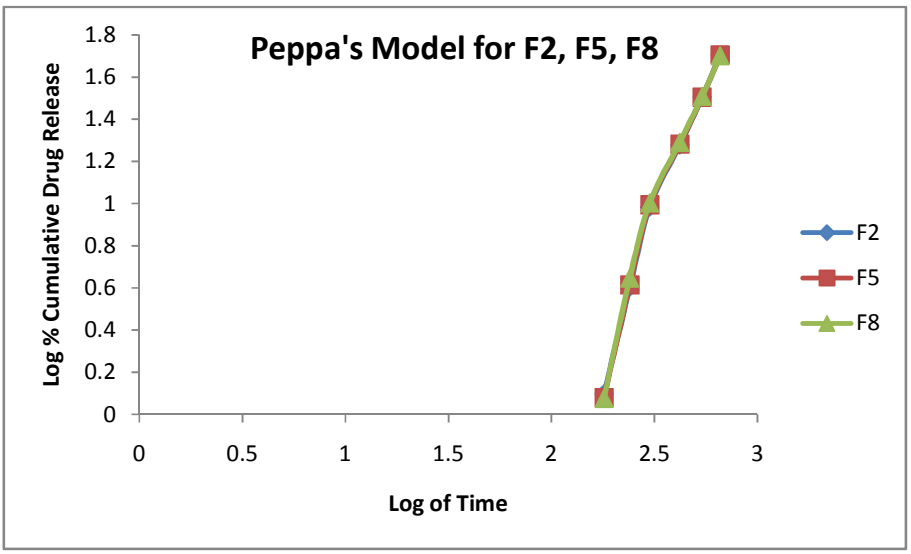
Graph 10: Shows higuchi model for F2, F5, F8



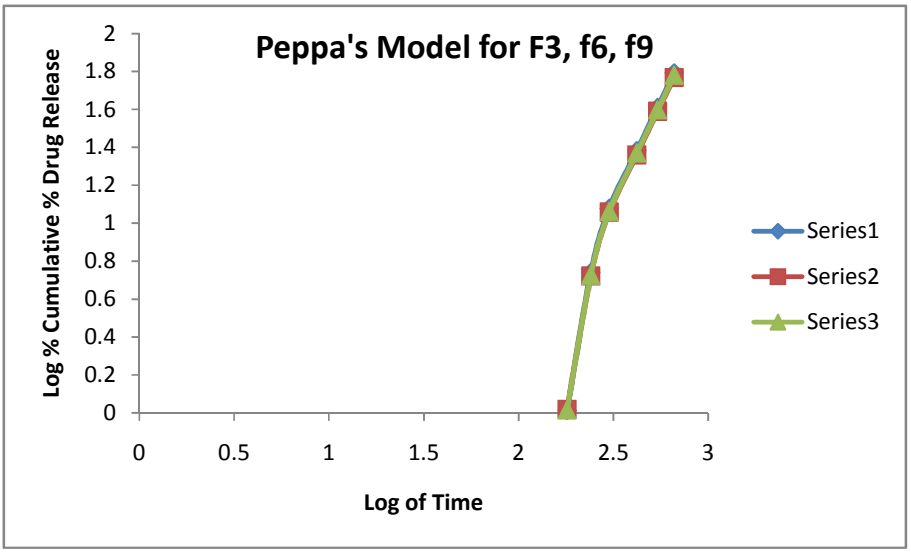
Graph 11: Shows higuchi model for F3, F6, F9



Graph 12: Shows peppa's model for F1, F4, F7



Graph 13: Shows peppa's model for F2, F5, F8



Graph 14: Shows peppa's model for F3, F6, F9

Curve fitting data of release rate profile of formulation F1 to F5

Table 22

METHOD		FORMULATION CODE				
		F1	F2	F3	F4	F5
Zero order	R^2	0.997	0.976	0.983	0.987	0.977
First order	R^2	0.954	0.927	0.936	0.950	0.925
Higuchi	R^2	0.744	0.623	0.633	0.691	0.625
Peppa's	R^2	0.922	0.973	0.943	0.919	0.969
	n	0.421	0.595	0.6388	4.794	0.599

Curve fitting data of release rate profile of formulation F6 to F9

Table 23

METHOD		FORMULATION CODE			
		F6	F7	F8	F9
Zero order	R^2	0.984	0.988	0.981	0.981
First order	R^2	0.923	0.948	0.923	0.924
Higuchi	R^2	0.635	0.694	0.633	0.633
Peppa's	R^2	0.947	0.917	0.963	0.947
	n	0.603	0.478	0.592	0.635

7.1.3. AFTER STABILITY STUDIES:

The Formulation F3 containing HPMC 4000 was selected for Stability studies for the period of three months. The following results were obtained:

TABLETING PROPERTIES OF BILAYER TABLETS OF F3 CONTAINING HPMC 4000 AFTER STABILITY STUDY

Table 24

S. No	Parameters	Formulation (F3 HPMC 4000)
1	Weight Variation	299±2.64
2	Hardness ± SD (kg/cm^3)	4.2±0.05
3	Friability ± SD (%)	0.652±0.006
4	Thickness ± SD (mm)	2.40±0.10
5	Disintegration Time (sec)	36±1.15
6	Drug Content	96.25±1.15
7	% Drug Release	91.96

8. DISCUSSION

8.1 Determination of Melting point of Carvedilol.

Melting point of both the drugs was found to be within the reported limit. It complies with standards thus indicating the purity of the drug sample.

8.2 Preparation of standard curve of Carvedilol :

From the standard curve of Carvedilol it was observed that the drug obeys beer's law in concentration range of 1-5 µg/ml in acid buffer (pH 1.2) and phosphate buffer (pH6.8).

8.3 Determination of IR spectrum of Carvedilol:

The FTIR spectral analysis showed that there was no appearance or disappearance of any characteristic peaks of pure drug of Carvedilol in the physical mixture of drug and polymer, which confirms the absence of chemical interaction between drug and polymers.

8.4 Formulation:

Nine formulations of sustained release bilayer tablets were prepared using polymers such as Eudragit RSPO, Ethyl cellulose, and HPMC 4000 in different concentrations and proportions by wet granulation technique in sustaining layer and sodium starch glycolate is used as super disintegrent in immediate release layer. All the formulations were prepared by keeping constant tablet weight (300 mg ± 20mg) and hardness (4.2 ± 0.5 kg/cm^2).

8.5 Evaluation parameters:

Physicochemical evaluation :

The granules were prepared by wet granulation method and preformulation studies were carried out. The granules of all the batches exhibited good flow characteristics evident from the results of their physicochemical evaluations. The angle of repose value ranged from $23^0$14" to $26^0$38". The results were found to be below 28^0 and hence the blend showed to have good flow ability. Bulk and tapped densities are used for the measurement of Compressibility index. The BD ranged from 0.689 to 0.769

while TD ranged from 0.769 to 0.869. The compressibility index (%) was calculated form the BD and it ranged from 10.344 to 14.814. The blend was found to have free flowing property as the result were found to be below 20%. The Hauser's ratio ranged from1.116 to 1.174. The result indicates the free flowing properties of the granules as the value was below 1.2.

The prepared tablets were subjected to evaluation tests such as hardness, thickness, % weight variation, friability and drug content. All the nine formulations had shown results for these characteristics within the acceptable ranges.

***In vitro* drug release profile:**

From the results of in vitro release study, it was observed that the release of Carvedilol from the prepared formulations was analyzed by plotting the cumulative percent drug released *vs*. time. Simple visual observation of the plot shows an initial burst effect. From all the formulations, over of the drug was released within 120 minutes of the dissolution study. This initial high amount of drug release can be attributed the immediate release layer of the formulation. Further release of drug was studied for 12 hrs. Eudragit RSPO, Ethyl cellulose and HPMC 4000 has been used as release retardant polymer in controlled release dosage forms. Ethyl Cellulose reduces the drug release due to a reduction in the penetration of the solvent molecules into the system because of the hydrophobic nature of ethyl cellulose present on the surface of the tablet, *i.e.* the rate of release is controlled by the permeability of matrix structure. Graph shows that formulation F1, F4, F7 containing HPMC 4000, Ethyl Cellulose, Eudragit RSPO could not sustain release beyond 40.53%, 62.17%, and 62.32% respectively over the period of 12 hrs. However, the formulation F3, F6, F9 containing HPMC 4000, ethyl cellulose and Eudragit RSPO which showed a release rate of 92.94%, 87.37% and 90.31% respectively. And hence F3 containing HPMC 4000 which showed a release rate of 92.94% was selected as optimized formulations, because they could sustain the release rate of drug for 12 hrs. As the formulation containing Eudragit RSPO swells more in aqueous medium and the release rate of F6 containing ethyl cellulose is less when compared to F3 HPMC 4000. Hence the formulation F3 containing HPMC 4000 is considered the optimized formulation.

The optimized formulation of F3 was compared with the marketed tablet of Carvedilol with respect to the *in-vitro* dissolution studies for its sustained action. The release rate of F3 was found to be nearly equal to the release rate of the marketed tablet.

Curve fitting data analysis:

The curve fitting results of the release rate profile of the designed formulations gave an idea on the mechanism of drug release. Data of *in vitro* release was fitted to various models like Korsmeyers-peppas, Zero order, First order, and Higuchi matrix. From the values for diffusion coefficient (n), it was found that all the formulations follows Fickian's release mechanism, except formulation HPMC 4000 which follows non-fickian's release mechanism.

RANGE FOR VALUE OF KORSMEYERS-PEPPAS MODEL FOR FORMULATIONS

Table 25

Krosmeyers-peppas	Range
R^2	0.8206 – 0.8529
Y	0.2322 – 0.2693
n	0.22-0.25

8.6.STABILITY STUDIES:

The results of stability study, which was carried for 90 days, showed that there was no significant change in colour; drug content, hardness, friability, disintegration time and *in vitro* drug. But just showed a slight decrease in the parameters which falls in the acceptable range.

9. SUMMARY AND CONCLUSION

9.1.SUMMARY:

Carvedilol is a non selective β-blocker antagonist, which is used in treatment of CHF and hypertension. Carvedilol is rapidly and completely absorbed in the gastrointestinal tract. Its elimination half-life is approximately 6 hours.

It is given as oral dosage form in the treatment of angina pectoris and the management of hypertension. Its short biological half-life 6 hrs and frequent administration (usually two times a day) make it a potential candidate for sustained release preparations. The bioavailability of Carvedilol is approximately 25-35%. Because of such pharmacokinetic characteristic the conventional dosage forms of the drug suffer the drawbacks of typical immediate release tablets. To overcome these drawbacks, sustained release tablets can be prepared.

In the present work efforts have been made to develop bilayer sustain release matrix tablet of Carvedilol, containing a fast releasing layer of Carvedilol prepared by wet granulation technique using sodium starch glycholate as a super disintegrant and a sustained releasing layer of Carvedilol prepared by wet granulation method using Eudragit RSPO, Ethyl Cellulose and HPMC 4000 in different ratios as sustaining polymers.

Prepared tablets were subjected to various evaluation parameters such as hardness, weight variation, % friability, thickness, disintegration, drug content, *invitro* drug release profile.

9.2.CONCLUSION:

The results of the experimental study confirm that the polymer concentration significantly influence the drug release. The tablets of optimized formulation F3 containing HPMC 4000 shown **92.94 %** drug release at the end of 12 hrs, this indicates that it can sustain the drug release till the desired time period. While the release rate of the marketed tablet was found to be **95.94%.**

Results discussed above showed that the tablet of all formulations has acceptable physical parameters. The *in vitro* release of all the formulations which was subjected to pharmacokinetic data analysis and found that formulations F3 follows Fickian's model as the best fitted model to the release profile of the formulations.

- Formulations F3 are found to be stable at accelerated stability as per the ICH guidelines for a period of 90 days.

Finally it can be concluded that with limited number of experiments an optimized formulation with desired drug release can be developed with appropriate experimental design and optimization technique.

Future scope of this study

Since the release rate of the marketed tablet and the optimized bilayer tablet is nearly equal and hence the work can be further extended to perform *in vivo – in vitro* correlation.

10. BIBLIOGRAPHY

1. Controlled Drug Delivery, fundamentals and applications, 2nd edition, Volume – 19, Joseph R Robinson, Page No., 373-421.
2. Fundamentals of controlled drug delivery: Influence of drug properties and routes of drug administration on the design of sustained and controlled release systems In: Robinson JR. Editors. Controlled drug delivery: fundamentals and applications. 2nd ed. Robinson JR., Lee VHL, Marcel Dekker Inc; New York: 2005, Page No., 3 - 94.
3. Essentials of controlled drug delivery In: S. P. Vyas. Editors. Controlled Drug Delivery – Concepts and Advances, S. P. Vyas, Roop. K. Khar, Vallabh Prakashan, Delhi. 2006, Page No., 1 – 53.
4. The Remington's Science and Practice of Pharmacy, 20th edition 2006, volume – 1 mack publishing company, Page No., 903-913, 939-941.
5. Sustained release dosage forms In: Herbert A. Lieberman. Editors. The Theory and Practice of Industrial Pharmacy, 3rd edition (Indian), Nicholas G. Lordi, Varghese publishing house; Mumbai. Page No., 430 – 456.
6. Sustained and Controlled Release Drug Delivery Systems In: Gilbert S. Banker. Editors, Modern Pharmaceutics, 4th edition revised and expanded, Gwen M. Jantzan, Joseph R. Robinson, Marcel Dekker Inc; New York. USA.2008 Page No., 503-530.

7. Oral Drug Delivery and Delivery Systems In: Novel Drug Delivery Systems, 2nd edition, Yie W. Chien, Marcel Dekker Inc; New York. USA.2007 Page No., 139 – 196.

8. Controlled Release Medication, A Textbook of Biopharmaceutics and pharmacokinetics A Treatise. 1st edition, Brahmankar DM, Jaiswal SB, Vallabh Prakashan, New Delhi: 1995, Page No., 64-70, 336-348.

9. Pharmaceutics – The Science of Dosage form Design, M.E.Aulton 2nd Edition.

10. Pharmaceutical Dosage Forms and Drug Delivery, Loyd V.Allen, Nicholas G. Popovich and Howard C.Ansen 8th Edition.

11. The Theory and Practice of Industrial Pharmacy, Keith Marshall, Compression and consolidation of powdered solids. In: Herbert A. Lieberman, Joseph L. Kanig, Leon Lachman, 3rd edition, (Indian), Varghese publishing house; Mumbai. Page No., 66 – 99.

12. The Theory and Practice of Industrial Pharmacy, Herbert A. Lieberman, Joseph L. Kanig, Leon Lachman. 3rd edition (Indian), Varghese publishing house; Mumbai. Page No., 297-300.

13. Formulation and Evaluation of Bilayer Sustained Release Tablets of Salbutamol and Theophyline. R.Nagaraju and Rajesh Kaza. International Journal of Pharmaceutical Sciences and Nanotechnology. 2, 2009.

14. Design and Evaluation of Sustained Release Tablets of Propranolol Hydrochloride. Chinam Niranjan Patra, Arethi Bharani Kumar, Hemant Kumar Pandit, Satya Prakash Singh, Meduri Vimala Devi. Acta Pharamaceutical Sciences. 479-489, 2007.

15. Congestive Heart Failure - Wikipedia, the Free Encyclopedia (a U.S. registered 501(c) (3) tax-deductible nonprofit charity.). Html.

16. Hypertension - Wikipedia, the Free Encyclopedia (a U.S. registered 501(c) (3) tax-deductible nonprofit charity.). Html, 14 October 2008.

17. British Pharmacopoeia 2007.

18. Rang and Dale's Pharmacology. H.P.Rang, M.M.Dale, J.M. Ritter,R.J.Flower. 6th edition.

19. Ethyl cellulose- Wikipedia, the Free Encyclopedia.

20. Chemistry of ethyl cellulose.The dow chemical company (1995-2009).

21. Eudragit RSPO, Handbook of Pharmaceutical Excipients, 3rd edition, Arthur H. Kibbe, Pharmaceutical Press. London. Page No., 305 – 308.

22. HPMC E-15, Wekipedia,the free encyclopedia.

23. Sodium Starch Glycholate, Handbook of Pharmaceutical Excipients. 3rd edition, Arthur H. Kibbe, Pharmaceutical Press. London. Page No., 501 – 504.

24. Yie W.Chien. Oral Drug Delivery Systems 2nd edition. Marcel Dekker Inc ; NewYork, USA, 2007.

25. Vogel's Textbook of Quantitative Chemical Analysis, 6th edition, J. Mendhan, R. C. Denney, J. D. Bames, M. J. K. Thomas, Page No., 720.

26. Robinson JR, Erikesen SP, Theoretical Formulation of Sustained release dosage forms. Journal of Pharmaceutical Sciences. 55. 1966.

27. Iranian Journal of Pharmaceutical Research (2009), Issue 8 (1), Development and evaluation of regioselective bilayer floating tablets of Atenolol and Lovastatin for biphasic release profile, Ajit Kulkarni and Manish Bhatia, Page No., 15-25.

28. Tropical Journal of Pharmaceutical Research August 2010; 9 (4): Development and Evaluation of Controlled-Release Bilayer Tablets Containing Microencapsulated Tramadol and Acetaminophen, MA Naeem, A Mahmood, SA Khan and Z Shahiq, Page No., 347-354.

29. Textbook of physical pharmaceutics. 2nd edition, C. V. S. Subramaniam, Vallabh Prakashan. Delhi. 2000, Page No., 180 - 234.

30. Physical Pharmacy-Physical Chemical Principles in the Pharmaceutical Sciences, 4th edition, Martin, P. Bustamante and A. Chun, Lippincott Williams and Wilkins, Baltimore 2002, Page No., 446–448.

31. International Journal of PharmTech Research, volume-2, April-June 2010, Formulation and Evaluation of Bilayered Tablets of Ibuprofen and Methocarbamol, Remya P.N, Damodharan. N, Sulakshan Kumar. C.V, Page No., 1250 – 1255.

32. "Mechanism of Solute Release from Porous Hydrophilic Polymers." International Journal of Pharmcy. 1983, Korsmeyer R. W., Gurny R. Peppas, Page No., 25-35.

33. "Mechanism of Sustained Action Medication: Theoretical Analysis of Rate of Release of Solid Drug Dispersed in Solid Matrix." Journal of Pharmceutical Sciences, 1963, Higuchi T, Page No., 1145-1149.